Effect of adaptive servo-ventilation for central sleep apnoea in systolic heart failure on muscle sympathetic nerve activity: a SERVE-HF randomised ancillary study

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Effect of Adaptive Servo-Ventilation for Central Sleep Apnoea in Systolic Heart Failure on Muscle Sympathetic Nerve Activity: a SERVE-HF Randomised Ancillary Study

Short title: Tamisier; Effect of ASV on MSNA in SERVE-HF

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One-sentence Summary

In patients with chronic heart failure (HF), the suppression of central sleep apnoea by adaptive servo-ventilation does not have a significant effect on chronic HF-related sympathetic activation and leads to increased cardiovascular mortality.

Take-home figure (Figure Abstract)

ABSTRACT

Rationale: Adaptive servo-ventilation (ASV) effectively suppresses central sleep apnoea (CSA) but has been associated with increased all-cause and cardiovascular mortality in chronic heart failure (HF) patients with reduced ventricular ejection fraction (HFrEF). All-cause and, especially, cardiovascular mortality in chronic HF is highly correlated with sympathetic tone. This analysis of SERVE-HF data investigated the effect of ASV on sympathetic tone in patients with HFrEF and CSA.

Methods: HFrEF patients in the SERVE-HF trial (left ventricular ejection fraction [LVEF] ≤45%, apnoea–hypopnea index [AHI] ≥15/h with predominant CSA) were randomly assigned to receive guideline-based HF treatment alone (controls) or plus ASV. For this analysis, the primary outcome was change in muscle sympathetic nerve activity (MSNA) at three-month follow-up. The effects of baseline MSNA and change in MSNA over time on mortality in the main study were also assessed.

Results: 40 patients with HFrEF were included in this analysis (age 71.3±11.7 years, LVEF 34.2±7.7%, 57.5% in NYHA class II, 42.5% in NYHA class III, AHI 35.2±11/hour). Sympathetic tone evolution during follow-up did not differ between groups (controls: 47.6±8.3 bursts/min at baseline to 44.6±11.2 bursts/min; ASV group: 43.0±9.0 to 42.74±9.45 bursts/min). The reduction in sympathetic tone was associated with significantly increased cardiovascular mortality in the ASV group, whereas in the control group reduced sympathetic tone appeared to be protective.

Conclusions: Suppression of CSA with ASV did not seem to have a significant effect on chronic HF-related sympathetic activation. Simultaneous suppression of CSA and reduction in MSNA was associated with increased cardiovascular mortality.

CLINICAL TRIAL REGISTRATION: http://clinicaltrials.gov: NCT00733343

KEY WORDS: adaptive servo-ventilation; central sleep apnoea; muscle sympathetic nerve activity; sympathetic tone; systolic heart failure

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INTRODUCTION

Central sleep apnoea (CSA) is an independent risk factor for increased hospitalisation and mortality in patients with heart failure and reduced ejection fraction (HFrEF) [1]. In the large, randomised SERVE-HF trial, the addition of adaptive servo-ventilation (ASV) to guideline-based therapy in patients with HFrEF and predominant CSA had no significant effect on the composite primary endpoint (time to death from any cause, or first life-saving cardiovascular intervention or unplanned hospitalisation for worsening heart failure) compared with guideline-based medical therapy alone (control) [2]. However, an increase in both all-cause and cardiovascular mortality was reported in the ASV group [2]. Specifically, in patients allocated to ASV, the risk for cardiovascular death without prior hospitalisation was significantly increased. This was presumably arrhythmia-related sudden death, and was seen in patients with the most impaired left ventricular function [3].

A key deleterious effect of CSA in heart failure patients is the occurrence of repeated bursts of sympathetic activity with each central event [4,5]. Specifically, in the presence of periodic breathing, sympathetic activity measured by MSNA increases during central apnoeas and decreases during hyperventilation phases [5]. The combination of intermittent hypoxia and micro-arousals produces nocturnal sympathetic over-activity, which in turn results in daytime chronic up-regulation of the sympathetic system,[6] aggravating the existing HFrEF-associated sympathetic activity burden. In the context of heart failure, increased sympathetic nervous system activity can trigger arrhythmias and has been linked with increased mortality in heart failure patients,[7-9] particularly sudden death.[10]

The association between increased sympathetic nervous system activity and increased morbidity, arrhythmias and mortality in heart failure patients, was the rationale for adding an assessment of muscle sympathetic nerve activity (MSNA) to the SERVE-HF study.

It was initially hypothesised that ASV would reduce sympathetic tone by normalising breathing during sleep. However, given the unexpected results of the SERVE-HF trial, the effects of the study interventions on MSNA have the potential to facilitate understanding of mechanisms underlying the excess cardiovascular mortality in patients allocated to ASV. Therefore, the aim of this single-centre ancillary study conducted within the SERVE-HF trial was to evaluate changes in MSNA over three months in the two SERVE-HF treatment groups (ASV and control). The prognostic value of baseline MSNA and changes in MSNA over time on mortality were also addressed.

METHODS

Design overview

The measurement and analysis of MSNA was a 3-month ancillary study to the SERVE-HF trial conducted in a single-centre in Grenoble, France. This ancillary study and the main serve-HF trial were approved by the local ethics committee, "CPP Sud-Est V", Grenoble, FRANCE (2008-A00414-51/2) and registered on clinicaltrials.gov (NCT00733343). All participants provided signed informed consent before inclusion in the trial. After the final MSNA study visit, all participants continued to be followed in the main SERVE-HF trial for at least 24 months. The MSNA study protocol was approved by the SERVE-HF steering committee. The trial and ancillary study were conducted in accordance with Good Clinical Practice guidelines and the principles of the 2002 Declaration of Helsinki.

Participants

Patients were eligible to participate if they met all SERVE-HF trial inclusion criteria, described in detail previously [2,11], and were willing to participate in the MSNA ancillary study. In

brief, patients were aged ≥22 years, had symptomatic chronic heart failure of ≥12 weeks duration (New York Heart Association [NYHA] class III or IV, or NYHA class II with at least one heart-failure-related hospitalisation in the preceding 24 months) with left ventricular ejection fraction (LVEF) ≤45%, were receiving stable guideline-based medical treatment, and had predominant CSA (apnoea-hypopnea index [AHI] ≥15 events/hour, with >50% central events [apnoea or hypopnea] and a central AHI of ≥10 events/hour). Inclusion criteria also required no change in NYHA class or medication dosage and no hospitalisation for worsening heart failure within the previous 4 weeks, and that a period of at least 6 months had elapsed since cardiac resynchronisation therapy (see the online supplement of the primary publication for full details [2]).

Procedures

Sleep studies

All patients had sleep apnoea diagnosed using overnight respiratory polygraphy (n=18) or polysomnography (n=22). A complete description of sleep recording and analysis is provided in the online supplement.

Randomisation and Interventions

In the SERVE-HF trial patients were randomised (1:1) to the ASV or control group using codes generated by a central computer. Allocation was performed using blocs and stratified by centre. There was no separate randomisation for the MSNA study. The SERVE-HF trial was open-label because of practical, scientific and ethical issues, and problems with investigator blinding associated with the delivery of sham pressure therapy. Details of ASV settings and titration are provided in the online supplement.

Main Outcome Measures

All outcome variables were measured at baseline (prior to ASV treatment) and again after 3 months of optimal medical therapy alone (control) or optimal medical therapy plus ASV. The primary outcome was change in sympathetic tone (assessed MSNA recordings) from baseline to 3 months. MSNA was measured using peroneal microneurography, considered the gold standard for determining sympathetic tone (see online supplement for full details). Secondary cardiovascular outcomes included changes in resting blood pressure, heart rate (RR interval), ultrasound popliteal arterial blood flow, and 24-hour urinary catecholamine levels. Clinical status was based on NYHA class; quality of life assessed using the Minnesota Living with Heart Failure questionnaire and the EuroQoL-5D; and sleepiness evaluated using the Epworth Sleepiness Scale score. Overall health and functioning were assessed using a visual analogue scale and 6-minute walk test, respectively.

Associations between baseline MSNA and change in MSNA over time, and the SERVE-HF primary outcome (combined outcome: all-cause death or first life-saving cardiovascular intervention or unplanned hospitalisation for worsening chronic heart failure), as well as with all-cause death, and cardiovascular death were tested.

Subgroup analysis

Due to the stronger association between ASV therapy and cardiovascular death in low ejection fraction patients reported in the main Serve-HF study and the suggestion of an exacerbated response in patients with very low ejection fraction (below 30%) [3], a subgroup comparison between patients having at inclusion a LVEF below or equal to and above 30% was also done.

Statistical analysis

This study was powered based on the MSNA outcome. At the time the analysis was designed, no data were available on the effect of continuous positive airway pressure (CPAP) or ASV on MSNA in HFrEF patients with CSA. One previous study showed that treatment with CPAP reduced MSNA by 10 bursts/min (17%) compared with controls in HFrEF patients with obstructive sleep apnoea (OSA) [12]. Because CSA and OSA have different underlying pathophysiologies, we assumed that ASV would decrease MSNA by ≤10 bursts/min (17%) and that there would be no change in the control group (standard deviation [SD] of 8). Assuming an α error of 5%, and statistical power of 90%, at least 16 patients per arm were required to detect a difference of 10 bursts/min between treatment groups.

Continuous variables are expressed as median (25^{th}/75^{th} percentiles) or mean (SD), and categorical variables are reported as absolute numbers and percentages. Baseline comparisons between groups were made using Student's t-test or Wilcoxon test, depending on the validation of normal distribution. For discrete variables, a Chi-squared or Fisher's exact test was used as appropriate. Normality of distribution was assessed using the Shapiro-Wilk test. All randomised patients were included in the intention-to-treat (ITT) analysis. The per-protocol population was defined as patients who completed the 3-month follow-up visit without any protocol deviation.

Differences between the ASV and control groups in change from baseline to 3-month follow-up were evaluated with a paired t-test. Unadjusted treatment effects and adjusted treatment effects were analysed using a mixed model with two factors (fixed factor: group, random factor: time) and by ANCOVA, respectively. In the ITT analysis, missing data were replaced by simple median imputations. Missing data from the patient who died before V2

were not imputed. Additional details of the per-protocol analysis are reported in the online supplement.

A Cox regression with Firth's penalised maximum likelihood bias reduction method was used for survival analysis due to the small sample size and the limited number of events. For continuous independent variables, results are presented as hazard ratio values for a one-unit increase in the independent variables within each randomisation group. Statistical significance of a difference in these hazard ratios is given as “p-value for interaction”. Data management and statistical analyses were performed using SAS® (version 9.2, OSA Institute, Cary, NC, USA) and R (3.2.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 48 patients were enrolled in the SERVE-HF trial in Grenoble between February 2008 and May 2013; one patient declined to participate in the MSNA study and baseline sympathetic nerve recordings were not available for seven patients (Figure 1). Therefore, 40 patients were included in the ITT analysis: 21 in the control group and 19 in the ASV group. Follow-up results were available for 39 patients because one patient in the control group died at 67 days. As permitted by the study protocol, two patients from the control group asked to start ASV. All patients were male and there were no statistically significant differences in baseline characteristics between the two treatment groups (Table 1). Sleep study data at baseline were also similar in the two groups (Table 2), apart from a lower proportion of central events and time spent with SpO_2 below 90% (T90) in the ASV group. After three months, mean ASV usage was 4.03±3.12 hours/night, including five patients who used ASV for <3 hours/night. As expected, there was a significant stabilisation of the

ventilatory pattern during sleep in the ASV group, with a marked decrease in the AHI based on data from the 3-month follow-up PSG/PG (Table 3).

Figure 1 and Tables 1, 2 and 3 about here

Primary outcome

In the ITT analysis, the evolution of sympathetic tone, assessed by MSNA recording, did not differ significantly between the ASV and control groups, either when sympathetic activity was expressed as bursts/minute or as bursts/100 heartbeats (Figure 2).

Secondary outcomes

There were no significant changes in twenty-four-hour urinary catecholamine levels (adrenaline, noradrenaline and dopamine) during the course of the study and no significant difference in levels between the ASV and control groups (Table 4). Overall heart failure status improved significantly from baseline in both the ASV and control groups, as shown by improvements in 6-minute walk distance, the Minnesota Living with Heart Failure Questionnaire score, a significant decrease in systolic blood pressure and an increase in arterial popliteal flow (Table 4).

Table 4 about here

Change in sympathetic activity over time

At baseline, sympathetic activity was significantly related to age, haemoglobin levels and the absence of beta-blocker use (Table 5). MSNA was also significantly associated with subjective sleepiness as assessed by the Epworth Sleepiness Scale and the frequency of daytime naps (Table 5). Sympathetic activity was not associated with any marker of CSA or hypoxia during sleep (Table 5).

Table 5 about here

Baseline MSNA and change in MSNA over the 3 months were considered as factors for long-term outcomes. In our SERVE-HF subgroup, median follow-up (analysed with r reverse Kaplan-Meier (KM)) was 3.61 years (95% CI 3.17; 4.79) with no significant difference in follow-up between the study arms (p=0.984). In the control group, higher baseline MSNA was associated with a significantly higher rate of the combined outcome (all-cause death or unplanned hospitalisation for worsening heart failure) (Figure 3A), and of all-cause death (Figure 3B) and cardiovascular death (Figure 3C). No such associations were seen in the ASV group. After 3 months' follow-up, an improvement in MSNA normalised for heart rate (bursts/100hb) was associated with significantly different outcomes in the two treatment groups (Figure 3C). In the control group, a decrease in sympathetic activity was associated with lower cardiovascular mortality but in the ASV group, a reduction in sympathetic tone was associated with higher mortality (Figure 3C).

Per-protocol and LVEF ≤30% versus >30% analyses

The results of the per-protocol (Tables S1, S2, S3, S4 and S5) and LVEF subgroup (Tables S6, S7 and S8) analyses did not differ markedly from those of the intention-to-treat analysis.

Discussion

The SERVE-HF intention-to-treat main analysis showed significantly increased all-cause and cardiovascular mortality in patients allocated to the ASV versus control group [2]. The present analysis of SERVE-HF data provides additional insights into these results by investigating sympathetic activity, a major component of arrhythmogenesis, cardiovascular morbidity and mortality in heart failure patients [7,13]. We found no greater reduction in

MSNA in the ASV group than in controls. For patients who had a reduction in sympathetic tone between baseline and 3 months cardiovascular mortality was increased in the ASV group but decreased in the control group.

Elevated sympathetic nervous activity and high catecholamine levels are a hallmark of HFrEF and both are independent predictors of higher mortality [7-9,13]. Moreover, MSNA and catecholamine levels are generally thought to be even further elevated in patients with HFrEF plus CSA-Cheyne Stokes respiration (CSR) [14,15]. This superimposed up-regulation of sympathetic tone is proposed to be a factor contributing to increased mortality in this patient subgroup. In HFrEF with CSA-CSR, the significant attenuation of central sympathetic activity by suppression of sleep apnoea was expected to provide a nonpharmacological intervention to complement drugs targeting the sympathetic nervous system. Previous studies have reported that abolition of OSA by CPAP treatment in cardiac failure patients lowered MSNA [12,15,16]. In our HFrEF patients with predominant CSA, ASV for three months did not reduce MSNA or catecholamine levels compared with controls despite suppression of nocturnal sleep-disordered breathing. These results differ from those of previous studies in similar populations, where CPAP [14,17] or ASV [18] have been reported to significantly decrease sympathetic tone and catecholamine levels. However, the results of another major SERVE-HF subgroup study , showing that ASV was not associated with any significant changes in cardiac structure or natriuretic peptide levels, are more consistent with our findings [19].

The association between periodic breathing and increased sympathetic activity has been recently challenged by some authors [20]. Analyses with adjustment for the severity of heart failure, suggest that the additional effect of CSA-CSR on sympathetic activity is trivial [21,22]. Hyperventilation and large tidal volumes are known to decrease or suppress MSNA [5].

During CSA-CSR, MSNA increases during central events but is counterbalanced by a decrease in sympathetic activity during hyperventilation. In our study, cardiac function, the main determinant of sympathetic activity, was not improved by ASV. Therefore, it was not surprising that MSNA was not reduced.

In cardiac failure, the elevated level of sympathetic activity plays a deleterious role over the long-term and is associated with progression of heart failure with adverse cardiac remodelling and poor outcomes. However, acute high sympathetic tone is also a compensatory mechanism that maintains cardiac output in HFrEF. Therefore, the abrupt suppression of sympathetic tone might counteract this benefit. Also, during the hyperventilation phase of periodic breathing, large variations in thoracic pressure may act as an additional cardiac pump facilitating maintenance of cardiac output by increasing the stroke volume [23]. A recent study investigating the hemodynamic effects of voluntary hyperventilation in healthy volunteers and patients with heart failure showed a significant increase in cardiac output and stroke volume in heart failure patients [24]. This could be evidence that CSA does in fact represent a positive compensatory response for the failing heart. A recent multistate model analysis of the SERVE-HF data revealed that the higher risk of cardiovascular death in patients with HFrEF and predominant CSA in the ASV group was mainly seen in those with the most impaired cardiac function (LVEF <30%) [3]. In our study, patients in the ASV group who showed a reduction in MSNA with suppression of CSA had a higher mortality. Similarly, in the MOXCON trial, central sympathetic inhibition with sustained-release moxonidine was shown to reduce mortality in heart failure patients [25]. While, the severity of heart failure in patients from the MOXCON [25] and SERVE-HF [2] trials was similar, a possible explanation for higher mortality in the MOXCON trial was suggested to be that the sympathetic inhibition was too fast [25]. ASV quickly and effectively

suppresses CSA, but this might stress a failing heart compared with the gradual titration of a beta-blocker that more progressively reduces sympathetic activity. One aspect, that was not assessed in all these patients was objective sleep quality. We recently demonstrated that ASV does not improve sleep quality, only sleep efficiency [26]. This lack of improvement in sleep quality may be related to an increase in the number of periodic leg movements during sleep (PLMS) and the PLMS-related arousal index [26].

The main limitation of our study was the small number of patients included, even though this subgroup was representative of the overall SERVE-HF study population. The small sample size meant that there was 3.5 kg/m² difference in baseline body mass index between the treatment groups despite randomisation. Given that SERVE-HF patients enrolled at our site were all male, the results of this analysis cannot necessarily be applied to females with the same condition. A study with a larger patient population including both males and females is warranted. Similarly, baseline characteristics of patients included in the present MSNA sub-study differed in some respects to the overall SERVE-HF population (Table S9). Body weight was lower in the MSNA cohort although body mass index was similar. This analysis included more patients in NYHA class I and with a longer 6-minute walk distance. There was a trend to a lower proportion of patients with dilated myocardiopathy (p=0.074), a higher proportion with cardiac resynchronisation devices with a defibrillator, and fewer who had a prescription for ACE inhibitors/angiotensin receptor blockers, aldosterone antagonists, diuretics and glycosides. Moreover, because SERVE-HF patients continued their standard medical treatment we cannot exclude the possibility that sympathetic activity was not blunted by one or more of many medications taken. Finally, our study explored peripheral sympathetic vascular tone, and it is possible that cardiac sympathetic tone may behave differently.

In conclusion, this SERVE-HF ancillary study conducted at one SERVE-HF centre found that sympathetic nervous system activity was not significantly reduced in the ASV group after 3 months of therapy. This suggests that CSA might not play a major role in inducing additional sympathetic activation in patients with HFrEF. Patients with HFrEF and predominant CSA who experienced both normalisation of central events during sleep and a reduction in MSNA were at increased risk of death. Overall, the way in which to effectively treat CSA in HFrEF patients remains unclear and requires further study.

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Data Sharing

Access to this subset of SERVE-HF study data is reviewed by and approved by the steering committee and study sponsor. For further information, please email rtamisier@chu-grenoble.fr

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CONFLICT OF INTEREST (COI) STATEMENT

Dr Renaud Tamisier reports receiving lecture fees from ResMed, and grant support through his institution from ResMed, Agiradom and Philips, and travel grants form Agiradom.

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Dr Helmut Teschler reports no conflict of interest.

Dr Martin Cowie reports no conflict of interest.

Dr Patrick Lévy reports no conflict of interest.

ROLES AND RESPONSIBILITIES OF EACH AUTHOR

Renaud Tamisier: concept and design, acquisition, analysis, or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, administrative, technical, or material support and supervision.

Jean-Louis Pepin: concept and design, acquisition, analysis, or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, administrative, technical, or material support and supervision.

Holger Woehrle: concept and design, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content.

Muriel Salvat: acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content.

Gilles Barone-Rochette: acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content.

Cécile Rocca: acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content.

Eik Vettorazzi: concept and design, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content.

Helmut Teschler: concept and design, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content.

Martin Cowie: concept and design, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content.

Patrick Lévy: concept and design, acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, administrative, technical, or material support and supervision.

Tables

Table 1. Baseline demographic and clinical characteristics, overall and by group.

	All (n=40)	Control (n=21)	ASV (n=19)
Age, years	73.8 [65.7; 78.6]	74 [67.8; 76.9]	69.1 [62.2; 82.5]
Male, n (%)	40 (100)	21 (100)	19 (100)
Body mass index, kg/m²	27.5 [23.3; 31.4]	28.3 [23.7; 31.5]	24.8 [21.9; 31.2]
Height, cm	170 [165.8; 175.3]	169 [165; 172]	171 [167; 176.5]
Weight, kg	75 [66; 92.3]	80 [70; 93]	70 [65.8; 88]
Type 2 diabetes, n (%)	10 (25)	6 (28.6)	4 (21.1)
LVEF, %	35 [30; 40]	36 [30; 40]	31 [28; 40]
NYHA class, n (%)			
II	23 (57.5)	11 (52.4)	12 (63.2)
III	17 (42.5)	10 (47.6)	7 (36.8)
6MWT, % predicted[#]	80.7 [74.5; 94.2]	79 [69.4; 97.9]	80.8 [74.8; 90.4]
HF aetiology, n (%)			
Dilated	7 (17.5)	5 (23.8)	2 (10.5)
Hypertensive	2 (5)	2 (9.5)	0 (0)
Ischaemic	26 (65)	12 (57.1)	14 (73.7)
Unknown	5 (12.5)	2 (9.5)	3 (15.8)
Left-bundle branch block*, n (%)	10 (66.7)	7 (77.8)	3 (50.0)
Heart rhythm, n (%)			
Sinus rhythm	27 (69.2)	12 (60.0)	15 (78.9)
Atrial fibrillation	6 (15.4)	3 (15.0)	3 (15.8)
Other	6 (15.4)	5 (25.0)	1 (5.3)
Implanted device, n (%)			
Non-CRT pacemaker	3 (12.0)	1 (8.3)	2 (15.4)
ICD	4 (16.0)	0 (0.0)	4 (30.8)
CRT-P	2 (8.0)	2 (16.7)	0 (0.0)
CRT-D	16 (64.0)	9 (75.0)	7 (53.8)
HF medication, n (%)			
Diuretics	29 (72.5)	16 (76.2)	13 (68.4)
Beta-blockers	37 (92.5)	19 (90.5)	18 (94.7)
ACEI or ARB	31 (77.5)	16 (76.2)	15 (78.9)
Aldosterone antagonist	12 (30)	5 (23.8)	7 (36.8)

Values are median [25th; 75th percentile], or number of patients (%).

*Assessed in patients without an implanted device. [#]Missing n=2.

6MWT, 6-minute walk test; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronisation therapy; CRT-D, CRT with defibrillator function; CRT-P, CRT with pacemaker function; HF, heart failure; ICD, implantable cardioverter–defibrillator; LVEF, left

ventricular ejection fraction (determined using echocardiography); NYHA, New York Heart Association.

Table 2. Baseline respiratory characteristics, overall and by SERVE-HF treatment group

	All (n=40)	**Control (n=21)**	**ASV (n=19)**	**p-value**
AHI, /h	36.7 [26.8; 44.4]	37.5 [29.4; 44]	29.9 [25.5; 44.8]	0.40
Central events, %	84.1 [70.5; 94]	93.8 [84; 97.4]	73.2 [66.3; 84.2]	**<0.01**
ODI, /h	37 [23.9; 45.9]	37 [25.3; 52.4]	37 [22.4; 44.6]	0.25
Mean SpO_2, %	93 [92; 94.4]	92.2 [91.9; 94]	93.8 [92; 94.9]	0.10
Minimum SpO_2, %	78 [73.5; 83]	81 [74; 83]	78 [73; 83]	0.57
Time with SpO_2 <90%, min	21.3 [7.6; 48.4]	43 [15.3; 66.8]	11.7 [3.9; 21.6]	**0.02**
CSR, n (%)	37 (92.5)	21 (100)	16 (84.2)	0.10

Values are median [25^{th}; 75^{th} percentile] or n (%).

AHI, apnoea-hypopnea index; CSR, Cheyne-Stokes respiration; ODI, oxygen desaturation index; SpO_2, digital pulse oxygen saturation.

Table 3. Respiratory effects of adaptive servo-ventilation therapy on treated patients (n=19)

	Baseline	**3 months**	**Difference**	**p-value**
AHI, /h	29.9 [25.5; 44.8]	8.8 [1.6; 21.3]	–20 [–28.3; –7.6]	**<0.0001**
ODI, /h	37 [22.4; 44.6]	21.8 [12.4; 44.2]	0 [–24.7; 6.6]	0.43
Mean SpO_2, %	93.8 [92; 94.9]	93.8 [92.6; 95]	0 [0; 1]	0.55
Minimum SpO_2, %	78 [73; 83]	82 [76; 88]	3 [0; 12]	0.08
Time with SpO_2 <90%, min	11.7 [3.9; 21.6]	10.4 [0.2; 19.6]	0 [–11.5;2.5]	0.82

Values are median [25^{th}; 75^{th} percentile].

AHI, apnoea-hypopnea index; ODI, oxygen desaturation index; SpO_2, digital pulse oxygen saturation.

Table 4. Secondary endpoint variables at baseline (n=40) and follow-up (n=39).

		Baseline	3 months	Difference	p-value		
					Group	Time	Interaction
Weight, kg	Control	80.1±14.8	79.5±13.5	–0.7±6.2	0.61	0.97	0.40
	ASV	77.0±16.4	77.7±16.4	0.7±3.2			
6MWT, % pred*	Control	81.6±21.0	89.1±18.1	7.5±13.5	0.91	**0.02**	0.21
	ASV	84.7±14.6	87.1±12.5	2.4±11.5			
6MWT, m	Control	367.9±91.8	390.6±115.5	17.3±90.6	0.11	0.36	0.64
	ASV	431.9±104.1	431.2±122.6	8.5±69.9			
LHFQ score	Control	22.0±14.2	19.4±14.1	–2.6±17.7	0.99	0.05	0.35
	ASV	24.5±15.7	17.0±13.0	–7.6±14.3			
ESS score*	Control	5.5 [4; 8.5]	4 [4; 6]	0 [–2; 1.5]	0.23	0.84	0.76
	ASV	5 [3; 9]	5 [2; 5]	0 [–3; 2]			
RR int, sec	Control	966.5±152.4	1014.3±109.8	47.7±124.3	0.65	0.11	0.57
	ASV	993.9±123.8	1016.7±88.7	22.8±146.6			
SBP, mmHg *	Control	125.9±22.1	114.5±16.2	–11.4±20.8	0.60	**0.04**	0.30
	ASV	119.5±23.1	115.5±15.3	–3.9±23.8			
DBP, mmHg *	Control	70.6±13.2	69.6±9.9	–1.1±12. 8	0.17	0.54	0.24
	ASV	64.7±9.8	68.0±7.1	3.4±10.3			
ABF, cm/sec	Control	3.6 [3.0; 3.8]	4.0 [3.5; 4.7]	0.3 [–0.1; 1.0]	0.94	**0.02**	0.62
	ASV	3.7 [3.1; 4.3]	4.2 [3.7; 4.5]	0.4 [–0.1; 1.1]			
Hb, g/dL	Control	13.9±1.6	13.5±1.7	–0.4±1.4	0.66	0.50	0.16
	ASV	13.5±1.1	13.6±1.3	0.1±0.7			
Creat, µmol/L	Control	122.0±33.6	118.7±27.5	–3.3±25.7	0.78	0.57	0.74
	ASV	123.1±31.0	122.2±30.8	–0.9±18.8			
24-hour urinary catecholamines, nmol/mmol of creatinine*							
Noradrenaline	Control	17.4 [11.9;28.3]	14.1 [11.3;26.3]	0 [–2.1; 3.7]	0.44	0.50	0.97
	ASV	18.7 [16.8; 24.1]	17.9 [13.1; 23.2]	0 [–1.3; 0]			
Adrenaline	Control	2.3±1.3	2.1±1.2	–0.2±1.4	0.87	0.37	0.73
	ASV	2.3±1.4	1.9±1.3	–0.4±1.1			
Dopamine	Control	72.6±45.5	66.1±36.7	–6.5±24.9	0.45	0.13	0.89
	ASV	84.8±28.0	77.0±29.6	–7.8±15.1			

Values are mean ± standard deviation or median [25th; 75th percentile].

6MWT, 6-minute walk test; ABF, arterial blood flow (Doppler); Creat, plasma creatinine; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; Hb, plasma haemoglobin; RR int, R-R interval (heart rate); LHFQ, Living with Heart Failure questionnaire; SBP, systolic blood pressure.
*Missing values: Epworth Sleepiness Scale score n=1; 6MWT n=2; MSNA n=5; SBP, DBP, RR int, arterial flow, 24-hour urinary catecholamines n=17.

Table 5. Determinants of sympathetic activity at baseline in all patients.

	Burst/min		Burst/100hb	
	Estimate (β) (95% CI)	**p-value**	**Estimate (β) (95% CI)**	**p-value**
Age	0.3 (0.08, 0.53)	**0.01**	0.47 (0.02, 0.92)	**0.04**
Naps	0.09 (0.01, 0.17)	**0.03**	0.06 (–0.11, 0.22)	0.48
ESS score	0.84 (0.1, 1.57)	**0.03**	0.28 (–1.21, 1.76)	0.71
Beta-blockers (no treatment)	10.87 (0.56, 21.19)	**0.04**	9.79 (–10.65, 30.24)	0.34
Amiodarone use	8.06 (–13, 29.13)	0.44	39.07 (0.9, 77.24)	**0.05**
Plasma haemoglobin*	–1.41 (–3.5, 0.69)	0.18	–4.13 (–7.96, –0.3)	**0.04**
Natremia*	–0.88 (–1.92, 0.16)	0.09	–0.83 (–3.09, 1.43)	0.46
Oxygen desaturation index	0.13 (0, 0.27)	0.06	0.14 (–0.12, 0.41)	0.28
Mean oxygen saturation	–1.09 (–2.74, 0.57)	0.19	–2.91 (–5.98, 0.15)	0.06

CI, confidence interval; ESS, Epworth Sleepiness Scale; hb, heart beats.

*Missing values: plasma haemoglobin 2; natraemia 8.

FIGURE LEGENDS

Figure 1. Study flow chart. ASV, adaptive servo-ventilation; EQ5D, EuroQol-5D; HF, heart failure; M-QOL, Minnesota Living with Heart Failure questionnaire; MSNA, muscle sympathetic nerve activity. Control group V2 results are for 20 patients because one patient died at 67 days.

Figure 2. Change in sympathetic tone measured using muscle sympathetic nerve activity (MSNA) expressed both in burst/minute (left panel) and burst/100 heart beats (hb; right panel). Illustrated MSNA and blood pressure raw signals from two patients (control: left panel: adapted servo-ventilation, right panel).

Figure 3. Relationship between sympathetic tone measured using muscle sympathetic nerve activity (MSNA) in the control and adaptive servo ventilation (ASV) groups and risk of: **A.** the primary endpoint (all-cause death or life-saving cardiovascular intervention or unplanned hospitalisation for worsening chronic heart failure; events in 7 (33.3%) and 7 (36.8%) patients in the control and ASV groups, respectively); **B.** all-cause death; events in 6 (28.6%) and 5 (26.3%) patients in the control and ASV groups, respectively; and **C.** cardiovascular death; events in 5 (23.8%) and 3 (15.8%) patients in the control and ASV groups, respectively. The bars represent 95% confidence intervals (CI). Cox regression with Firth's penalised maximum likelihood bias reduction method was applied. For continuous independent variables (IV), results are presented as hazard ratio (HR) values for a one-unit increase in the IV within the randomisation group. Statistical significance of a difference in those HR values is given as “p-value for interaction”.

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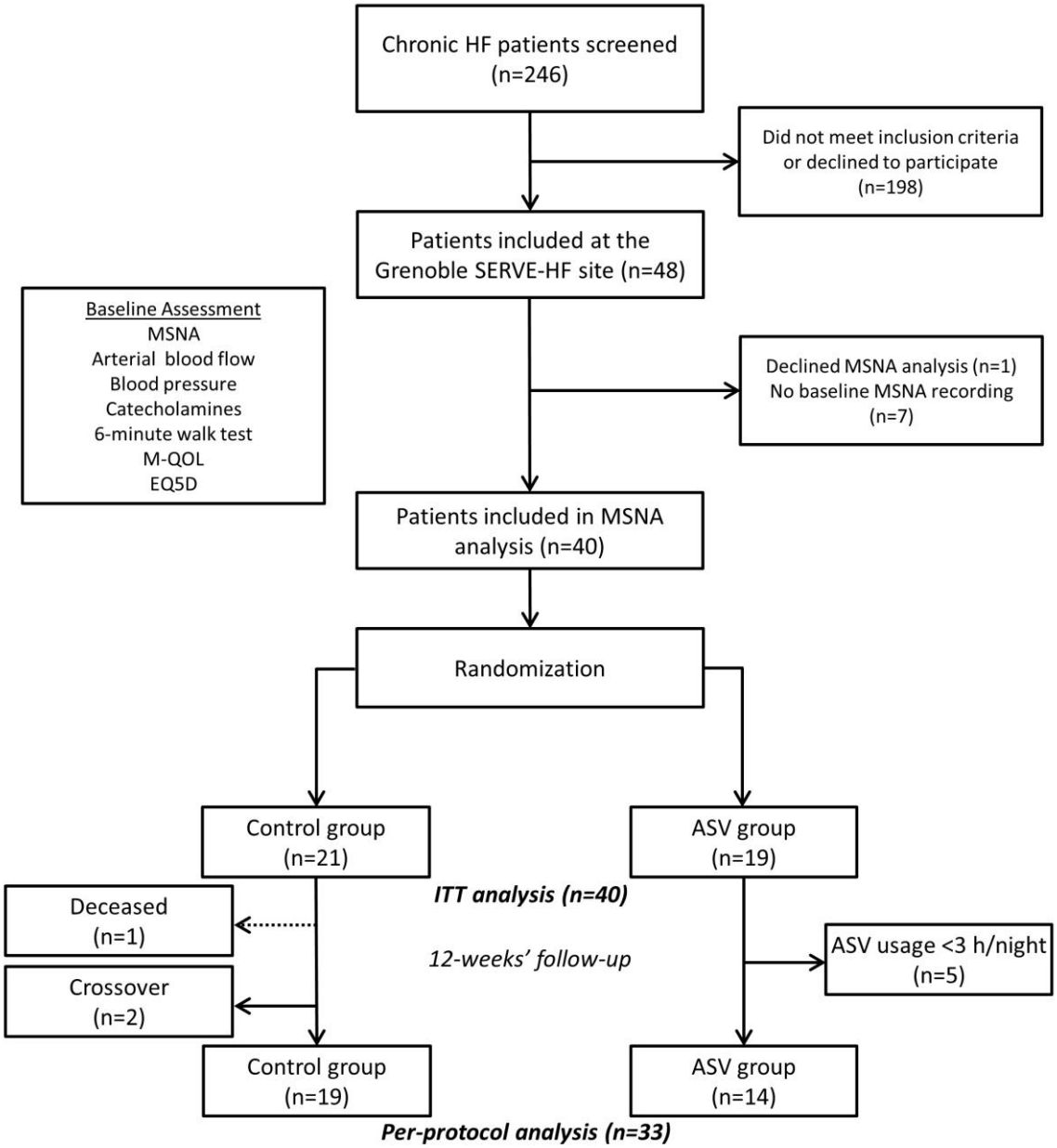
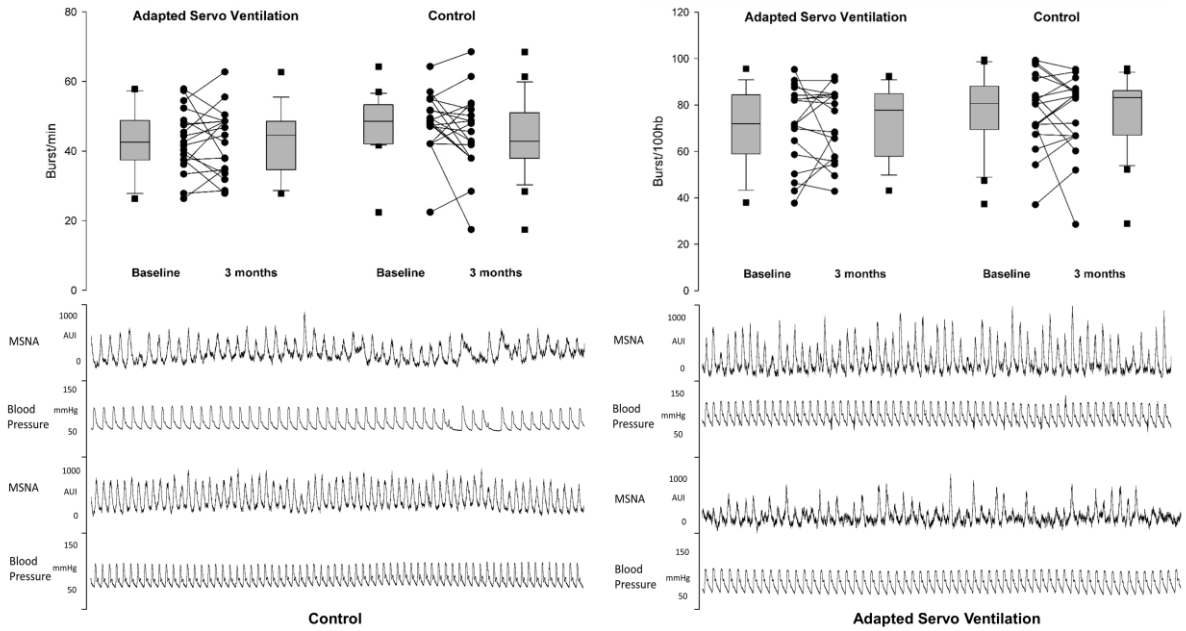
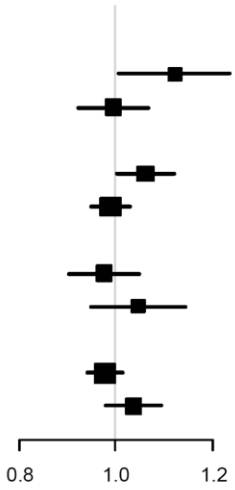
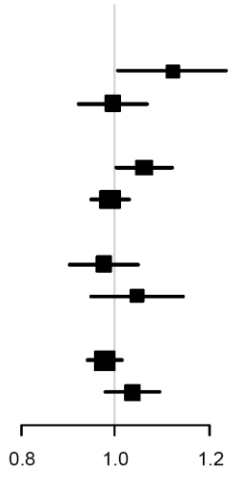

Chronic HF patients screened (n=246)
Did not meet inclusion criteria or declined to participate (n=198)
Patients included at the Grenoble SERVE-HF site (n=48)
Baseline Assessment
MSNA
Arterial blood flow
Blood pressure
Catecholamines
6-minute walk test
M-QOL
EQ5D
Declined MSNA analysis (n=1)
No baseline MSNA recording (n=7)
Patients included in MSNA analysis (n=40)
Randomization
Control group (n=21)
ASV group (n=19)
ITT analysis (n=40)
Deceased (n=1)
12-weeks' follow-up
ASV usage <3 h/night (n=5)
Crossover (n=2)
Control group (n=19)
ASV group (n=14)
Per-protocol analysis (n=33)


Adapted Servo Ventilation
Control
Burst/min
Burst/100hb
Baseline
3 months
MSNA
AUI
Blood Pressure
mmHg
Control
Adapted Servo Ventilation

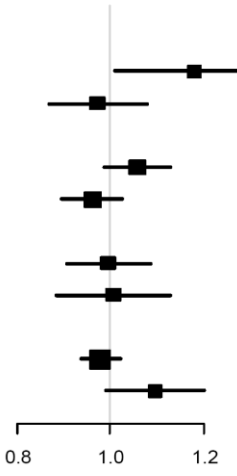
Variable	HR	95% CI	p-value for interaction
Resting MSNA (Burst/min) at BL			0.062
Control	1.14	(1.01, 1.30)	
ASV	0.99	(0.92, 1.08)	
Resting MSNA (Burst/100hb) at BL			0.025
Control	1.07	(1.00, 1.14)	
ASV	0.99	(0.95, 1.03)	
Change in Resting MSNA (Burst/min)			0.249
Control	0.97	(0.90, 1.05)	
ASV	1.05	(0.94, 1.17)	
Change in Resting MSNA (Burst/100hb)			0.089
Control	0.97	(0.94, 1.01)	
ASV	1.04	(0.98, 1.11)	

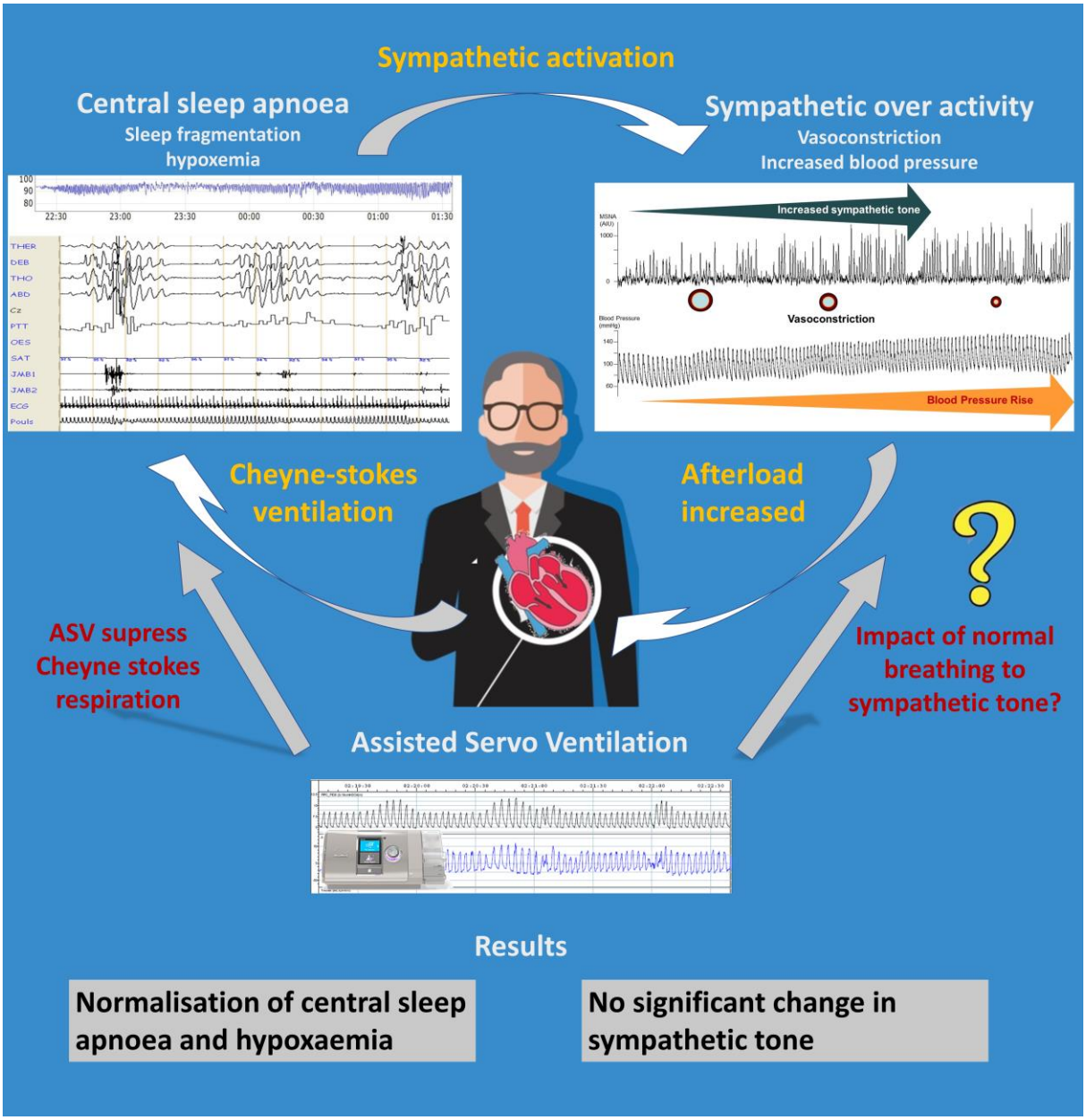


Variable	HR	95% CI	p-value for interaction
Resting MSNA (Burst/min) at BL			0.062
Control	1.14	(1.01, 1.30)	
ASV	0.99	(0.92, 1.08)	
Resting MSNA (Burst/100hb) at BL			0.025
Control	1.07	(1.00, 1.14)	
ASV	0.99	(0.95, 1.03)	
Change in Resting MSNA (Burst/min)			0.249
Control	0.97	(0.90, 1.05)	
ASV	1.05	(0.94, 1.17)	
Change in Resting MSNA (Burst/100hb)			0.089
Control	0.97	(0.94, 1.01)	
ASV	1.04	(0.98, 1.11)	



Variable	HR	95% CI	p-value for interaction
Resting MSNA (Burst/min) at BL			0.028
Control	1.22	(1.01, 1.47)	
ASV	0.97	(0.86, 1.09)	
Resting MSNA (Burst/100hb) at BL			0.024
Control	1.07	(0.99, 1.15)	
ASV	0.96	(0.89, 1.03)	
Change in Resting MSNA (Burst/min)			0.894
Control	1.00	(0.90, 1.10)	
ASV	1.01	(0.88, 1.15)	
Change in Resting MSNA (Burst/100hb)			0.035
Control	0.98	(0.93, 1.02)	
ASV	1.11	(0.99, 1.25)	





In chronic heart failure patients, the suppression of central sleep apnoea by Adaptive Servo-Ventilation does not have a significant effect on chronic HF-related sympathetic activation and leads to increased cardiovascular mortality.

Supplementary Material

Effect of Adaptive Servo-Ventilation for Central Sleep Apnoea in Systolic Heart Failure on Muscle Sympathetic Nerve Activity: a SERVE-HF Randomised Ancillary Study

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PROTOCOL AND MEASUREMENTS

Sleep study

For polysomnography, continuous recordings were taken with electrode positions C3/A2-C4/A1-Cz/01 of the international 10–20 Electrode Placement System; eye movements, chin electromyogram and ECG with a modified V2 lead were recorded. Events were scored manually according to standard criteria.[12] Cardio-respiratory polygraphy included at least the following signals: nasal pressure, oral and nasal thermistor, thoracic and abdominal movements, oxygen saturation (SpO_2), three lead electrocardiogram and body position. For polysomnography and polygraphy, airflow was measured with nasal pressure prongs together with the sum of oral and nasal thermistor signals. Respiratory effort was monitored using abdominal and thoracic bands. Oxygen saturation was measured using a pulse oximeter. An apnoea was defined as the complete cessation or a reduction by at least 90% of airflow for at least 10 seconds. An hypopnea was defined as a reduction of at least 50% in the nasal pressure signal or a decrease of between 30% and 50% associated with either oxygen desaturation of ≥3%, both for PSG and PG, or an EEG arousal (only for PSG) both lasting for at least 10 seconds.[12] Apnoeas were classified as obstructive, central or mixed according to the presence or absence of respiratory effort. The classification of hypopneas as obstructive or central was based on the thoraco-abdominal band signal and the shape of the respiratory nasal pressure curve (flow limited aspect or not). The AHI was defined as the number of apnoeas and hypopneas per hour of sleep (full polysomnography) or per hour of recording (polygraphy without EEG recording).

Physiologic measurements

A standard 3-lead electrocardiogram was recorded continuously throughout the study session. Beat-by-beat arterial blood pressure was measured via finger photoplethysmography (CNAP 500, CNSystems, Austria) and calibrated against oscillometric brachial pressures measured throughout the study session (automatic device calibration). Multiunit postganglionic muscle sympathetic activity was recorded from the peroneal nerve. Neural activity was amplified, the band pass was filtered, rectified and integrated to create the sympathetic neurogram for real-time inspection. The raw, unfiltered neurogram was recorded at 10 kHz and processed using our algorithm for identification of sympathetic nerve signals. Subjects were instrumented for measurement of blood flow velocity in the popliteal artery (4-MHz probe; EZdop, DWL) at the popliteal fossa of the leg contralateral to the nerve recording.

Muscle Sympathetic Nerve Activity (MSNA)

We obtained nerve recordings using standard tungsten microelectrodes inserted into the peroneal nerve posterior to the popliteal fossa, after localization by surface stimulation. Signals were filtered, amplified and full-wave rectified. The rectified signal was integrated for display on an oscilloscope and for recording (Nerve Traffic Analyzer, Model 662c-3, University of Iowa, Bioengineering Dept., Iowa City, IA). Electrode position in muscle sympathetic fibres was confirmed by pulsed synchronous bursts of activity occurring with a predictable delay after the QRS complex, reproducible activation during phase two of Valsalva's manoeuvre, elicitation of afferent nerve activity by mild muscle stretching, and the absence of response to startle. After acquisition of a suitable sympathetic nerve recording, a 5-minute resting baseline recording was obtained for analysis of MSNA, blood

pressure and popliteal artery blood flow. All signals were digitized and stored (Windaq, DATAQ Instruments) for subsequent analysis.

Sympathetic bursts were identified using a specific algorithm described by Hamner and colleagues[1] using Matlab software (The Mathworks Inc., Natick, MA USA). For purposes of quantification, MSNA was averaged over the 5-minute period and expressed as burst frequency (bursts/min), burst frequency normalized by heart beat (burst/100 hb), and burst amplitude (AUI/min). Blood pressure and blood flow were analysed as described previously.[2,3]

Management of ASV pressure support

Adjustment of ASV was performed in the hospital with the use of polysomnographic or polygraphic monitoring. Default settings were used (expiratory positive airway pressure 5 cmH_2O; minimum pressure support 3 cmH_2O; and maximum pressure support 10 cmH_2O). The expiratory positive airway pressure was increased manually to control obstructive sleep apnoea, and maximum pressure support was increased to control CSA. Patients were advised to use the ASV device for at least 5 hours per night, 7 days per week. Adherence to therapy was defined as the use of ASV for an average of at least 3 hours per night. The target was to reduce the AHI to <10 events/hour within 14 days after starting ASV.

RESULTS

Per-protocol analysis

The per-protocol analysis included 33 patients; excluded patients were two from the control group who crossed over to the ASV arm during the study and five from the ASV group who had device usage of <3 h/night. The results of the per-protocol analysis did not differ markedly from those of the intention-to-treat analysis (Tables S1, S2, S3, S4 and S5).

Subgroup analysis (below and above 30% of LVEF)

A subgroup analysis has been performed in patients below and strictly above 30% of LVEF. They were distributed as follows: Control LVEF ≤30%, n=7; Control LVEF >30%, n=14; ASV LVEF ≤30%, n=9; and ASV LVEF >30%, n=10. No significant difference was found between these groups except by design for LVEF (Table S6). The same higher proportion of central events as was described in the entire population was found in the ASV groups (Table S7). The primary outcome, sympathetic activity, did not change significantly between groups at follow-up (Table S8). As reported in the main analysis, there were increases in the 6-minute walking test (6MWT) and improvement in quality of life in all groups without difference between groups, or interaction for quality of life, but with an interaction for 6MWT due to an improvement only in the patients with LVEF>30 % (Table S8). No difference was found in the urinal catecholamines (Table S8).

Table S1. Baseline demographic and clinical characteristics for patients in the per-protocol analysis

	All	Control (n=19)	ASV (n=14)
Age, years	74 [66; 80.6]	74 [66; 77.4]	75.7 [66; 83.4]
Male sex, n (%)	33 (100)	19 (100)	14 (100)
Body mass index, kg/m²	28.3 [24; 31.5]	28.3 [23.7; 31.5]	28.2 [24; 32.3]
Type 2 diabetes, n (%)	10 (30.3)	6 (31.6)	4 (28.6)
LVEF, %	35 [30; 40]	35 [30; 40]	32.5 [30; 40]
NYHA class, n (%)			
II	19 (57.6)	11 (57.9)	8 (57.1)
III	14 (42.4)	8 (42.1)	6 (42.9)
6MWT, % of predicted	80.5 [69.4; 97.1]	78.6 [64.4; 91.4]	85.8 [77.9; 97.1]
Heart failure aetiology, n (%)			
Dilated	6 (18.2)	4 (21.1)	2 (14.3)
Hypertensive	2 (6.1)	2 (10.5)	0 (0)
Ischaemic	22 (66.7)	11 (57.9)	11 (78.6)
Unknown	3 (9.1)	2 (10.5)	1 (7.1)
Implanted device, n (%)			
CRT, ICD	14 (42.4)	8 (42.1)	6 (42.9)
Non-CRT pacemaker	5 (15.2)	3 (15.8)	2 (14.3)
Beta-blockers, n (%)			
Yes	30 (90.9)	17 (89.5)	13 (92.9)
No	3 (9.1)	2 (10.5)	1 (7.1)
ACEI or ARB, n (%)			
Yes	24 (72.7)	14 (73.7)	10 (71.4)
No	9 (27.3)	5 (26.3)	4 (28.6)
Aldosterone antagonist, n (%)			
Yes	10 (30.3)	5 (26.3)	5 (35.7)
No	23 (69.7)	14 (73.7)	9 (64.3)

Values are median [25^{th}; 75^{th} percentile], or number of patients (%).

6MWT, 6-minute walk test; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASV, adaptive servo-ventilation; CRT, cardiac resynchronization therapy; ICD implantable cardioverter–defibrillator; LVEF, left ventricular ejection fraction (determined using echocardiography); NYHA, New York Heart Association.

Table S2. Baseline respiratory characteristics for patients in the per-protocol analysis

	All	Control (n=19)	ASV (n=14)	p-value
AHI, events/h	37.5 [27; 44]	37.5 [27; 44]	37.8 [26.5; 44.8]	0.75
Central events, %	84.2 [69.9; 95.4]	94.1 [73.1; 97.5]	74.4 [65.5; 84.2]	**0.01**
ODI, events/h	37 [25.3; 45.7]	32.8 [22.2; 52.5]	39.8 [27.7; 44.6]	0.51
Mean SpO_2, %	93 [91.9; 94]	92.1 [91.6; 94]	93.5 [92; 94.6]	0.25
Minimal SpO_2, %	81 [75; 83]	81 [68; 83]	79 [75; 83]	0.96
Time with SpO_2 <90%, min	23 [12.1; 53.1]	43 [15.3; 80.6]	15.6 [7.4; 36.1]	0.07
CSR, n (%)	31 (93.9)	19 (100)	12 (85.7)	0.17

Values are median [25^{th}; 75^{th} percentile], or number of patients (%).
AHI, apnoea-hypopnoea index; ASV, adaptive servo-ventilation; CSR, Cheyne Stokes respiration; ODI, oxygen desaturation index; SpO_2, oxygen digital pulse saturation.

Table S3. Respiratory effects of adaptive servo-ventilation therapy in the per-protocol analysis

	Baseline	3 months	Change	p-value
AHI, events/h	37.8 [26.5; 44.8]	10.7 [5.9; 21.3]	–18.1 [–27.4; –9.6]	**0.0004**
ODI, events/h	39.8 [27.7; 44.6]	20.9 [14; 46.5]	–1.6 [–25.6; 12.6]	0.9
Mean SpO_2, %	93.5 [92; 94.6]	93 [92; 93.7]	0 [–1.4; 0.95]	0.91
Minimal SpO_2, %	79 [75; 83]	82.5 [78.5; 87.5]	3.5 [–1.5; 8.5]	0.23
Time with SpO_2 <90%, min	15.6 [7.4; 36.1]	15.1 [2.3; 43.5]	0.8 [–22.9; 17.8]	0.97

Values are median [25^{th}; 75^{th} percentile], or number of patients (%).
AHI, apnoea-hypopnoea index; ODI, oxygen desaturation index; SpO_2, oxygen digital pulse saturation.

Table S4. Secondary endpoint variables at baseline and follow-up in the per-protocol analysis.

		Baseline	3 months	Difference	p-value		
					Group	Time	Interaction
Weight, kg	Control	81.47±13.5	80.87±12.4	0.56±2.24	0.99	**0.01**	0.18
	ASV	81.68±16.51	83±16.72	1.5±3.15			
6MWT, % of predicted	Control	76.63±20.01	86.91±19.42	8.5±14.33	0.37	0.15	0.04
	ASV	86.91±16.97	85.57±13.5	–1.81±10.12			
Minnesota LHFQ score	Control	21.16±14.22	18.71±15.8	–1.57±17.52	0.62	0.19	0.50
	ASV	25.57±14.37	19.42±15.52	–6.33±13.64			
ESS score	Control	6 [4; 9]	4.5 [4; 6]	0 [–1; 2]	0.32	0.34	0.50
	ASV	5 [3; 9]	3.5 [1.5; 7.5]	–1 [–3.5; 0.5]			
Muscle sympathetic nerve activity							
Bursts/min	Control	48.88±8.67	49.44±9.62	0.68±4.45	0.052	0.83	0.86
	ASV	42.75±9.54	41.9±11.07	–0.5±9.56			
Bursts/100hb	Control	77.22±18.99	83.77±11.09	1.18±10.13	0.27	0.79	0.40
	ASV	73.1±16.98	69.64±16.72	–0.87±16.23			
RR interval, sec	Control	950.65±177.47	1034.14±128.37	15.27±87.1	0.25	0.69	0.25
	ASV	1028.49±112.02	1005.61±103.31	–15.96±102.34			
SBP, mmHg	Control	125.96±23.89	116.6±17.99	–4.13±14.98	0.58	0.18	0.90
	ASV	121.92±24.81	114.91±15.32	–4.26±24.07			
DBP, mmHg	Control	71.87±13.73	69.9±11.62	1.25±8.06	0.07	0.67	0.69
	ASV	63.74±7.72	66.84±5.52	0.87±8.79			
Arterial flow, cm/s	Control	3.69±1.59	4.68±1.84	0.98±1.83	0.78	**0.02**	0.52
	ASV	3.82±1.37	4.22±1.18	0.73±0.84			
Plasma haemoglobin, g/dL	Control	13.72±1.52	13.28±1.65	–0.38±1.32	0.60	0.46	0.24
	ASV	13.72±1.02	13.77±1.37	0.11±0.68			
Plasma creatinine, µmol/L	Control	126.42±34.74	117.25±28.67	–4.56±22.8	0.73	0.31	0.75
	ASV	121.29±32.12	119.62±33.33	–3.31±21.88			

Urine 24–hour catecholamines, nmol/mmol of creatinine							
Noradrenaline	Control	20.3 [19.2; 26.8]	22.9 [22.5; 31.3]	7.3 [–4.3; 10.9]	0.57	0.73	0.46
	ASV	20.9 [17.3; 24.1]	20.3 [16; 23.2]	–1.3 [–3.8; 2.3]			
Adrenaline	Control	2.9±1.36	2.37±1.55	–0.53±2.29	0.43	0.88	0.80
	ASV	2.03±1	1.81±1.11	–0.22±1.41			
Dopamine	Control	83.59±50.18	74.5±26.06	–9.09±38.36	0.69	0.20	0.86
	ASV	91.81±8.12	77.73±12.63	–14.08±20.11			

Values are median [25th; 75th percentile] or mean ± standard deviation.

6MWT, 6-minute walk test; ASV, adaptive servo-ventilation; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; LHFQ, Living with Heart Failure Questionnaire; SBP, systolic blood pressure.

DBP, SBP and arterial flow were measured using Doppler popliteal arterial blood flow velocity.

	Bursts/min		Bursts/100hb	
	Estimate (β) (95% CI)	**p-value**	**Estimate (β) (95% CI)**	**p-value**
Age	0.52 (0.2, 0.83)	**<0.01**	0.67 (0.01, 1.34)	**0.05**
Naps	0.1 (0, 0.2)	**0.05**	0.05 (–0.15, 0.25)	0.62
ESS score	0.67 (–0.3, 1.64)	0.17	–0.34 (–2.32, 1.65)	0.73
Beta-blockers (no treatment)	10.65 (–0.6, 21.91)	*0.06*	8.57 (–14.01, 31.15)	0.44
Amiodarone use	8.06 (–14.88, 31.01)	0.48	39.07 (–2.15, 80.28)	*0.06*
Plasma haemoglobin	–3.17 (–5.98, –0.37)	**0.03**	–8.07 (–12.97, –3.17)	**<0.01**
Natraemia	–1.14 (–2.28, 0)	**0.05**	–0.65 (–3.29, 1.99)	0.61
Oxygen desaturation index	0.13 (–0.04, 0.3)	0.12	0.12 (–0.21, 0.45)	0.45
Mean oxygen saturation	–0.92 (–3.08, 1.24)	0.39	–2.24 (–6.3, 1.83)	0.27

Table S5. Determinants of sympathetic activity at baseline in the per-protocol analysis

CI, confidence interval; ESS, Epworth Sleepiness Scale.

Table S6. Baseline demographic and clinical characteristics in patient subgroups based on left ventricular ejection fraction in the intention-to-treat analysis

	Control		ASV		
	LVEF ≤30% (n=7)	**LVEF >30% (n=14)**	**LVEF ≤30% (n=9)**	**LVEF >30% (n=10)**	**p value**
Age, years	74 [71; 76.9]	73.8 [63.2; 77.4]	68.1 [58.5; 80.6]	71.3 [65.4; 84.2]	0.92
Male sex, n (%)	7 (100)	14 (100)	9 (100)	10 (100)	NS.
BMI, kg/m²	28.3 [23.3; 31.5]	28.2 [24.8; 32.2]	24 [22.7; 28.7]	26.9 [21.9; 31.2]	0.59
Type 2 diabetes, n (%)	2 (28.6)	4 (28.6)	2 (22.2)	2 (20)	NS.
LVEF, %	27 [25; 30]	40 [36; 40]	28 [25; 30]	40 [40; 41]	<.01
NYHA class, n (%)					
II	1 (14.3)	10 (71.4)	5 (55.6)	7 (70)	0.08
III	6 (85.7)	4 (28.6)	4 (44.4)	3 (30)	.
6MWT (% of predicted) *	85.7 [78.3; 91.4]	78.2 [64.4; 101.1]	88.2 [80.5; 97.1]	79.1 [74.1; 85.7]	0.45
Heart failure aetiology, n (%)					
Dilated	2 (28.6)	3 (21.4)	2 (22.2)	0 (0)	0.37
Hypertensive	1 (14.3)	1 (7.1)	0 (0)	0 (0)	.
Ischemic	4 (57.1)	8 (57.1)	7 (77.8)	7 (70)	.
Unknown	0 (0)	2 (14.3)	0 (0)	3 (30)	.
Implanted device, n (%)					
CRT, ICD	5 (71.4)	4 (28.6)	6 (66.7)	4 (40)	0.18
Non-CRT pacemaker	0 (0)	3 (21.4)	1 (11.1)	1 (10)	0.74
Beta-blockers, n (%)	6 (85.7)	13 (92.9)	8 (88.9)	10 (100)	0.68
ACEI or ARB, n (%)	4 (57.1)	12 (85.7)	8 (88.9)	7 (70)	0.38
Aldosterone antagonist, n (%)	2 (28.6)	3 (21.4)	4 (44.4)	3 (30)	0.71

Values are median [25th; 75th percentile], or number of patients (%).

6MWT, 6-minute walk test; ACEI, angiotensin-converting enzyme inhibitor; ASV, adaptive servo-ventilation; ARB, angiotensin receptor blocker; ASV, adaptive servo-ventilation; CRT, cardiac resynchronization therapy; ICD implantable cardioverter–defibrillator; LVEF, left ventricular ejection fraction (determined using echocardiography); NYHA, New York Heart Association.

*Imputed variables

Table S7. Baseline respiratory characteristics in patient subgroups based on left ventricular ejection fraction in the intention-to-treat analysis

	Control		ASV		
	LVEF ≤30% (n=7)	**LVEF >30% (n=14)**	**LVEF ≤30% (n=9)**	**LVEF >30% (n=10)**	**p-value**
AHI, events/h	31 [22.2; 37.7]	41.8 [32.6; 47.6]	28.1 [27.5; 45.2]	33.7 [24.4; 38.3]	0.33
Central events, %	**89.9 [73.1; 97.4]**	**94.6 [85.1; 97.5]**	**77.7 [65.5; 85.2]**	**71.7 [66.7; 83.1]**	**0.01**
ODI, events/h	29.8 [16.6; 37]	42 [28.1; 52.5]	41 [31; 44.6]	35.7 [22.4; 43.3]	0.33
Mean SpO_2, %	93.8 [92; 94]	92.1 [91.6; 93]	94.5 [92; 95]	93.5 [92; 94]	0.34
Minimal SpO_2, %	77 [66; 84]	81 [74; 83]	76 [75; 80]	80 [73; 84]	0.70
Time with SpO_2 <90%, min	21 [12.5; 43.2]	48.4 [23; 80.6]	14.1 [3.9; 21.6]	9.8 [5; 21.6]	0.08
CSR, min	31 (93.9)	19 (100)	12 (85.7)	31 (93.9)	0.27

Values are median [25^{th}; 75^{th} percentile], or number of patients (%).
AHI, apnoea-hypopnoea index; ASV, adaptive servo-ventilation; CSR, Cheyne Stokes respiration; ODI, oxygen desaturation index; SpO_2, oxygen digital pulse saturation.

Table S8. Sympathetic activity, secondary endpoint, and plasma parameters and urinary catecholamine variables at baseline and follow-up by treatment group in patient subgroups based on left ventricular ejection fraction in intention to treat analysis (sympathetic activity: Control LVEF≤30%, n=7; Control LVEF >30%, n=14; ASV LVEF ≤30%, n=9; and ASV LVEF >30%, n=10; secondary endpoints: Control LVEF≤30%, n=7; Control LVEF >30%, n=14; ASV LVEF ≤30%, n=9; and ASV LVEF >30%, n=10; plasma parameters and urinary catecholamines: Control LVEF ≤30%, n=3; Control LVEF >30%, n=9; ASV LVEF ≤30%, n=5; and ASV LVEF >30%, n=7)

		Baseline	3 months	Difference	p-value		
					Group	Time	Interaction
Sympathetic activity variables							
Bursts/min	Control LVEF ≤30%	48.48±3.93	44.17±9.49	–4.31±7.1	0.66	0.16	0.53
	Control LVEF >30%	47.71±9.87	44.33±12.04	–3.38±10.08			
	ASV LVEF ≤30%	43.2±11.64	44.61±10.34	1.41±5.07			
	ASV LVEF >30%	42.87±6.49	41.07±8.77	–1.8±9.91			
Bursts/100hb	Control LVEF ≤30%	76.92±18.01	76.19±11.84	–0.73±15	0.84	0.99	0.87
	Control LVEF >30%	76.12±16.58	74.81±18.28	–1.31±15.86			
	ASV LVEF ≤30%	70.94±21.23	74.45±13.14	3.51±12.29			
	ASV LVEF >30%	71.72±13.51	70.26±17.41	–1.46±16.34			
RR interval, sec	Control LVEF ≤30%	949.03±203.06	1012.2±109.76	63.17±150.83	0.92	0.08	0.88
	Control LVEF >30%	958.89±136.9	1014.13±109.92	55.24±124.18			
	ASV LVEF ≤30%	982.59±128.14	1014.94±107.62	32.35±191.29			
	ASV LVEF >30%	1002.75±125.75	1018.26±73.6	15.51±103.22			
SBP, mmHg	Control LVEF ≤30%	138.5±19.22	115.63±13.66	–22.86±24.33	0.38	**0.01**	0.22
	Control LVEF >30%	119.56±20.33	113.52±17.21	–6.04±16.11			
	ASV LVEF ≤30%	118.09±29.22	110.51±9.51	–7.58±24.71			
	ASV LVEF >30%	120.7±17.37	120.03±18.37	–0.66±23.78			
DBP, mmHg	Control LVEF ≤30%	72.62±17.16	68.68±4.24	–3.95±15.4	0.54	0.79	0.34
	Control LVEF >30%	70.71±11.54	69.95±11.61	–0.76±12.04			
	ASV LVEF ≤30%	63.42±12.35	69.9±5.06	6.48±10.41			

	ASV LVEF >30%	66±7.5	66.35±8.45	0.35±9.94			
Arterial flow, cm/s	Control LVEF ≤30%	3.43 [3.01; 3.71]	4.03 [3.87; 4.03]	0.31 [0.18; 0.96]	0.58	**0.03**	0.58
	Control LVEF >30%	3.71 [2.97; 3.9]	4.16 [3.26; 4.78]	0.48 [–0.17; 1.53]			
	ASV LVEF ≤30%	3.39 [2.99; 3.71]	4.18 [3.72; 4.18]	0.47 [0.13; 1.11]			
	ASV LVEF >30%	3.83 [3.32; 4.64]	4.18 [3.71; 4.95]	0.34 [–0.62; 0.88]			
Secondary endpoints							
Weight, kg	Control LVEF ≤30%	81.43±14.58	78.71±11.63	–2.71±10.3	0.75	0.52	0.58
	Control LVEF >30%	80.57±15.53	79.31±14.35	–1.26±6.72			
	ASV LVEF ≤30%	73.78±15.12	73.83±15.01	0.05±3.72			
	ASV LVEF >30%	79.8±17.78	81.1±17.67	1.3±2.62			
6MWT, % of predicted	Control LVEF ≤30%	81.08±17.8	78.45±14.64	–2.62±5.5	0.64	**0.04**	**0.01**
	Control LVEF >30%	79.84±23.66	94.2±17.08	14.37±14.08			
	ASV LVEF ≤30%	90.52±13.66	87.44±12.55	–3.07±10.77			
	ASV LVEF >30%	79.45±14.03	86.83±13.14	7.37±10.18			
Minnesota LHFQ	Control LVEF ≤30%	26.71±18.06	20.93±15.38	–5.79±23.02	0.84	**0.04**	0.70
	Control LVEF >30%	19.5±11.18	18.43±13.33	–1.07±14.4			
	ASV LVEF ≤30%	24.89±13.49	15.89±10.59	–9±13.53			
	ASV LVEF >30%	24.2±18.13	17.9±15.42	–6.3±15.58			
ESS score	Control LVEF ≤30%	8 [4; 13]	4 [4; 6]	–2 [–7;0]	0.30	0.46	0.09
	Control LVEF >30%	5 [4; 7]	4.5 [4; 6]	0 [–1; 2]			
	ASV LVEF ≤30%	6 [5; 9]	5 [4; 5]	–1 [–4; 0]			
	ASV LVEF >30%	3 [1; 8]	3.5 [2; 10]	0.5 [–1; 4]			
Plasma and urinary catecholamines							
Plasma haemoglobin, g/dL	Control LVEF ≤30%	13.51±1.66	12.86±1.15	–0.66±0.91	0.68	0.46	0.47
	Control LVEF >30%	13.98±1.6	13.83±1.75	–0.15±1.54			
	ASV LVEF ≤30%	13.43±0.95	13.59±0.93	0.16±0.63			
	ASV LVEF >30%	13.46±1.19	13.57±1.61	0.11±0.81			
Plasma creatinine, µmol/L	Control LVEF ≤30%	140.14±30.48	129±14.47	–11.14±31.66	0.46	0.35	0.72
	Control LVEF >30%	116.14±34.26	114.29±30.65	–1.86±23.67			

	ASV LVEF ≤30%	126.33±24.66	128.5±24.76	2.17±12			
	ASV LVEF >30%	120.2±36.85	116.6±35.75	–3.6±23.74			
Noradrenaline,	Control LVEF ≤30%	10.85 [8.05; 39.33]	10.85 [8.05; 62.12]	0 [0; 22.79]	0.90	0.82	0.72
nmol/mmol of creatinine	Control LVEF >30%	19.23 [15.25; 26.81]	15.25 [12.98; 22.91]	0 [–4.31; 0]			
	ASV LVEF ≤30%	20.95 [18.45; 24.05]	20.3 [16.78; 23.2]	0 [–3.75; 0]			
	ASV LVEF >30%	17.27 [13.1; 19]	16 [13.1; 19]	0[0;0]			
Adrenaline,	Control LVEF ≤30%	2.43±1.39	1.5±0.37	–0.93±1.61	0.73	0.20	0.30
nmol/mmol of creatinine	Control LVEF >30%	2.21±1.28	2.32±1.33	0.1±1.38			
	ASV LVEF ≤30%	2.2±1.37	1.26±0.53	–0.94±1.27			
	ASV LVEF >30%	2.37±1.62	2.61±1.62	0.24±0.53			
Dopamine,	Control LVEF ≤30%	62.27±22.43	71.02±33.6	8.76±15.17	0.85	0.35	0.47
nmol/mmol of creatinine	Control LVEF >30%	76±51.68	64.45±39.47	–11.56±26.1			
	ASV LVEF ≤30%	81.84±21.1	69.52±22.43	–12.33±20.23			
	ASV LVEF >30%	87.69±36.01	84.51±36.49	–3.18±7.11			

Values are median [Q1; Q3], mean ± standard deviation, or number of patients (%).

6MWT, 6-minute walk test; ABF, arterial blood flow (Doppler); DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; Hb, plasma haemoglobin; LHFQ, Living with Heart Failure questionnaire; SBP, systolic blood pressure.

Table S9. Baseline characteristics of patients included in the sympathetic nerve activity (SNA) substudy compared with patients not in the SNA substudy

	All other patients (n=1,285)	**SNA cohort (n=40)**	**p-value**
Age, years	69.4±9.9	71.3±11.7	0.231
Male, n (%)	1,158 (90.1)	40 (100.0)	**0.037**
Body mass index, kg/m²	28.6±4.9	27.4±4.8	0.122
Weight, kg	28.6±4.9	27.4±4.8	0.008
LVEF, %	32.3±8.0	33.8±7.6	0.235
NYHA class, n (%)			**<0.001**
≤II	366/1276 (28.7)	23 (57.5)	
≥III	910/1276 (71.3)	17 (42.5)	
Systolic blood pressure, mmHg	122.2±19.2	121.9±23.7	0.919
Diastolic blood pressure, mmHg	73.5±11.3	72.7±13.1	0.646
Dilated cardiomyopathy, n (%)	496/1273 (39.0)	10 (25.0)	0.074
HF aetiology, n (%)			0.388
Ischaemic	730/1255 (58.2)	26 (65.0)	
Other	525/1255 (41.8)	14 (35.0)	
Left-bundle branch block*, n (%)	139/584 (23.8)	5/15 (33.3)	0.394
Heart rhythm, n (%)			0.334
Sinus rhythm	740/1257 (58.9)	27/39 (69.2)	
Atrial fibrillation	319/1257 (25.4)	6/39 (15.4)	
Other	198/1257 (15.8)	6/39 (15.4)	
Implanted device, n (%)			**0.035**
Non-CRT pacemaker	58/701 (8.3%)	3/25 (12.0%)	
ICD	320/701 (45.6%)	4/25 (16.0%)	
CRT-P	33/701 (4.7%)	2/25 (8.0%)	
CRT-D	290/701 (41.4%)	16/25 (64.0%)	
Haemoglobin, g/dL	13.9±1.6	13.6±1.4	0.356
Creatinine, mg/dL	1.4±0.6	1.4±0.4	0.898
eGFR, mL/min/1.73m^2	58.8±21.0	57.0±20.3	0.586
6-minute walk distance, m	334.0±127.2	398.3±101.8	**0.002**
HF medication, n (%)			
Diuretics	192 (14.9)	11 (27.5)	**0.030**
Beta-blockers	1,186 (92.3)	37 (92.5)	0.962
ACEI or ARB	1,184 (92.1)	32 (80.0)	**0.006**
Aldosterone antagonist	656 (51.1)	28 (70.0)	**0.018**
Glycosides	272/1283 (21.2)	1 (2.5)	**0.004**
Antiarrhythmics	214 (16.7)	3 (7.5)	0.123

Values are median [25th; 75th percentile], or number of patients (%).

Data were missing for the following numbers of patients in the ‘All other’ group: body weight (n=17); body mass index (n=17); LVEF (n=256); systolic blood pressure (n=26); diastolic blood pressure (n=27); haemoglobin (n=52); creatinine (n=59); eGFR (n=180); and 6-minute walk distance (n=73). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronisation therapy; CRT-D, CRT with defibrillator function; CRT-P, CRT with pacemaker function; HF, heart failure; ICD, implantable cardioverter–defibrillator; LVEF, left ventricular ejection fraction (determined using echocardiography); NYHA, New York Heart Association.