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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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 https://bit.ly/3CfoLl6

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Abstract

Background 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 patients with reduced ventricular ejection fraction (HFrEF). All-cause and, especially, cardiovascular mortality in chronic heart failure 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–hypopnoea index (AHI) ⩾15 events·h^{-1} with predominant CSA) were randomly assigned to receive guideline-based heart failure treatment alone (controls) or plus ASV. For this analysis, the primary outcome was change in muscle sympathetic nerve activity (MSNA) at 3-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 New York Heart Association (NYHA) Functional Class II, 42.5% in NYHA Functional Class III, AHI 35.2±11 events·h^{-1}). Sympathetic tone evolution during follow-up did not differ between groups (controls: 47.6±8.3 bursts·min^{-1} at baseline to 44.6±11.2 bursts·min^{-1}; ASV group: 43.0±9.0 bursts·min^{-1} at baseline to 42.74±9.45 bursts·min^{-1}). 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 heart failure-related sympathetic activation. Simultaneous suppression of CSA and reduction in MSNA was associated with increased cardiovascular mortality.

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 end-point (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 muscle sympathetic nerve activity (MSNA) increases during central apnoeas and decreases during hyperventilation phases [5]. The combination of intermittent hypoxia and micro-arousals produces nocturnal sympathetic overactivity, which in turn results in daytime chronic upregulation 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 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 3 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 at 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) Functional Class III or IV, or 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–hypopnoea index (AHI) ⩾15 events·h^{-1}, with >50% central events (apnoea or hypopnoea) and a central AHI of ⩾10 events·h^{-1}). Inclusion criteria also required no change in NYHA Functional 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 supplementary material for full details [2]).

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 supplementary material.

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 supplementary material.

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 using MSNA recordings) from baseline to 3 months. MSNA was measured using peroneal microneurography, considered the gold standard for determining sympathetic tone (see supplementary material for full details). Secondary cardiovascular outcomes included changes in resting blood pressure, heart rate (RR interval), ultrasound popliteal arterial blood flow and 24-h urinary catecholamine levels. Clinical status was based on NYHA Functional Class; quality of life was assessed using the Minnesota Living with Heart Failure Questionnaire and the EuroQoL-5D; and sleepiness was evaluated using the Epworth Sleepiness Scale score. Overall health and functioning were assessed using a visual analogue scale and 6-min walk test, respectively.

Associations between baseline MSNA and change in MSNA over time and the SERVE-HF primary end-point (combined: 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 (<30%) [3], a subgroup comparison was also done between patients having a LVEF <30% or ⩾30% at inclusion.

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^{-1} (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^{-1} (17%) and that there would be no change in the control group (standard deviation 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^{-1} between treatment groups.

Continuous variables are expressed as median (interquartile range (IQR)) or mean with standard deviation, and categorical variables are reported as absolute number (percentage). Baseline comparisons between groups were made using the t-test or Wilcoxon test, depending on the validation of normal distribution. For discrete variables, the Chi-squared test 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 the 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 the 3-month follow-up visit were not imputed. Additional details of the per-protocol analysis are reported in the supplementary material.

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 1-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 (SAS Institute, Cary, NC, USA) and R version 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 oxygen saturation measured by pulse oximetry (S_{pO_2}) <90% (T_{90}) in the ASV group. After 3 months, mean±SD ASV usage was 4.03±3.12 h per night, including five patients who used ASV for <3 h per night. As expected, there was a significant stabilisation of the ventilatory pattern during sleep in the ASV group, with a marked decrease in AHI based on data from the 3-month follow-up polysomnography/polygraphy (table 3).

Primary outcome

In the ITT analysis, the evolution of sympathetic tone, assessed by MSNA recordings, did not differ significantly between the ASV and control groups, either when sympathetic activity was expressed as bursts per minute (bursts·min^{-1}) or as bursts per 100 heart beats (bursts·100 hb^{-1}) (figure 2).

Secondary outcomes

There were no significant changes in 24-h urinary catecholamine levels (adrenaline, noradrenaline and dopamine) during the course of the study, and no significant difference in levels between the ASV and

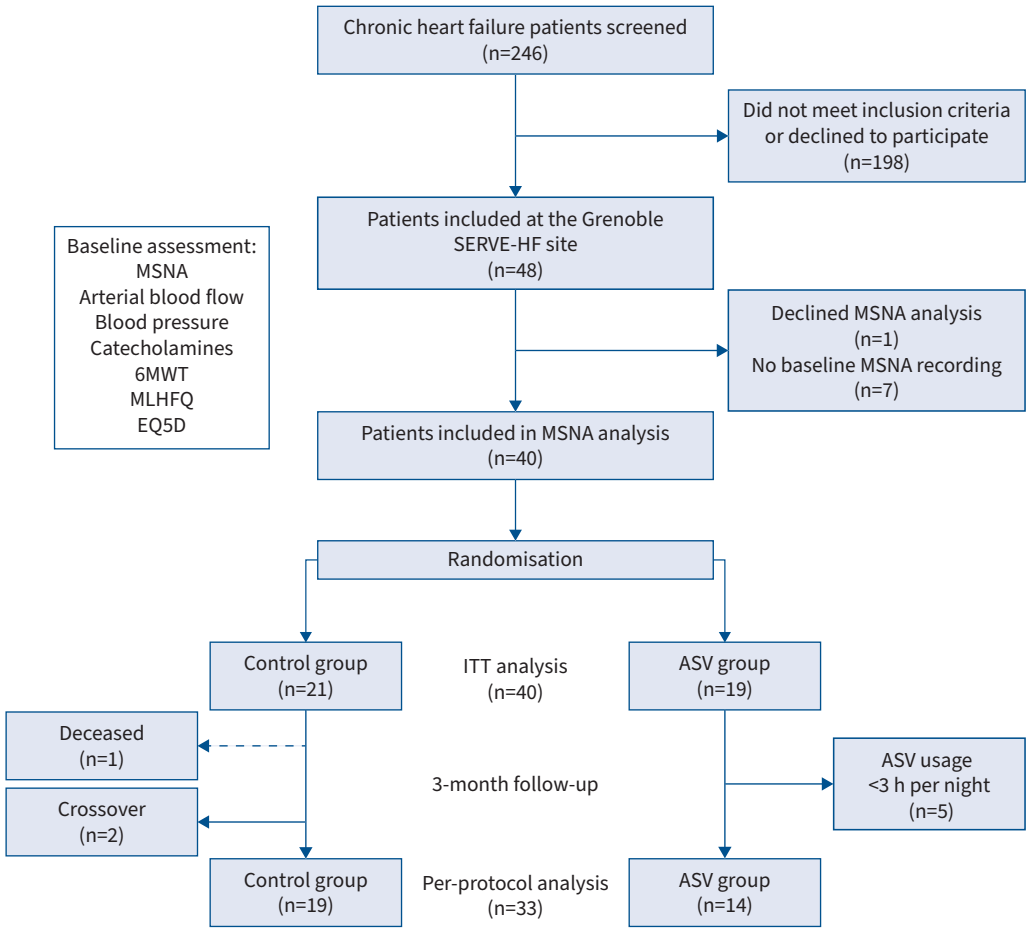

FIGURE 1 Study flowchart. MSNA: muscle sympathetic nerve activity; 6MWT: 6-min walk test; MLHFQ: Minnesota Living with Heart Failure Questionnaire; EQ5D: EuroQol-5D; ASV: adaptive servo-ventilation. Control group 3-month follow-up visit results are for 20 patients because one patient died at 67 days.

TABLE 1 Baseline demographic and clinical characteristics: overall and by treatment 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	40 (100)	21 (100)	19 (100)
BMI, kg·m^{-2}	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	10 (25)	6 (28.6)	4 (21.1)
LVEF, %	35 (30–40)	36 (30–40)	31 (28–40)
NYHA Functional Class			
II	23 (57.5)	11 (52.4)	12 (63.2)
III	17 (42.5)	10 (47.6)	7 (36.8)
6MWT, % pred[#]	80.7 (74.5–94.2)	79 (69.4–97.9)	80.8 (74.8–90.4)
Heart failure aetiology			
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[¶]	10 (66.7)	7 (77.8)	3 (50.0)
Heart rhythm			
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			
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)
Heart failure medication			
Diuretics	29 (72.5)	16 (76.2)	13 (68.4)
β-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)

Data are presented as median (interquartile range) or n (%). BMI: body mass index; LVEF: left ventricular ejection fraction (determined using echocardiography); NYHA: New York Heart Association; 6MWT: 6-min walk test; CRT: cardiac resynchronisation therapy; ICD: implantable cardioverter–defibrillator; CRT-P: CRT with pacemaker function; CRT-D: CRT with defibrillator function; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker. [#]: missing n=2; [¶]: assessed in patients without an implanted device.

control groups (table 4). Overall heart failure status improved significantly from baseline in both the ASV and control groups, as shown by improvements in 6MWD and the Minnesota Living with Heart Failure Questionnaire score, and a significant decrease in systolic blood pressure and an increase in arterial popliteal flow (table 4).

TABLE 2 Baseline respiratory characteristics: overall and by treatment group

	All (n=40)	Control (n=21)	ASV (n=19)	p-value
AHI, events·h^{-1}	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, events·h^{-1}	37 (23.9–45.9)	37 (25.3–52.4)	37 (22.4–44.6)	0.25
Mean S_{pO_2}, %	93 (92–94.4)	92.2 (91.9–94)	93.8 (92–94.9)	0.10
Minimum S_{pO_2}, %	78 (73.5–83)	81 (74–83)	78 (73–83)	0.57
Time with S_{pO_2} <90%, min	21.3 (7.6–48.4)	43 (15.3–66.8)	11.7 (3.9–21.6)	**0.02**
CSR	37 (92.5)	21 (100)	16 (84.2)	0.10

Data are presented as median (interquartile range) or n (%), unless otherwise stated. AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; S_{pO_2}: oxygen saturation measured by pulse oximetry; CSR: Cheyne–Stokes respiration. Significance (p<0.05) is indicated in bold.

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

	Baseline	3 months	Difference	p-value
AHI, events·h^{-1}	29.9 (25.5–44.8)	8.8 (1.6–21.3)	−20 (−28.3—7.6)	**<0.0001**
ODI, events·h^{-1}	37 (22.4–44.6)	21.8 (12.4–44.2)	0 (−24.7–6.6)	0.43
Mean S_{pO_2}, %	93.8 (92–94.9)	93.8 (92.6–95)	0 (0–1)	0.55
Minimum S_{pO_2}, %	78 (73–83)	82 (76–88)	3 (0–12)	0.08
Time with S_{pO_2} <90%, min	11.7 (3.9–21.6)	10.4 (0.2–19.6)	0 (−11.5–2.5)	0.82

Data are presented as median (interquartile range), unless otherwise stated. AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; S_{pO_2}: oxygen saturation measured by pulse oximetry. Significance (p<0.05) is indicated in bold.

Change in sympathetic activity over time

At baseline, sympathetic activity was significantly related to age, haemoglobin levels and the absence of β-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).

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 reverse Kaplan–Meier) was 3.61 (95% CI 3.17–4.79) years 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 end-point (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-month follow-up, an improvement in MSNA normalised for heart rate (bursts per 100 heart beats) was associated with significantly different end-points in the two treatment groups

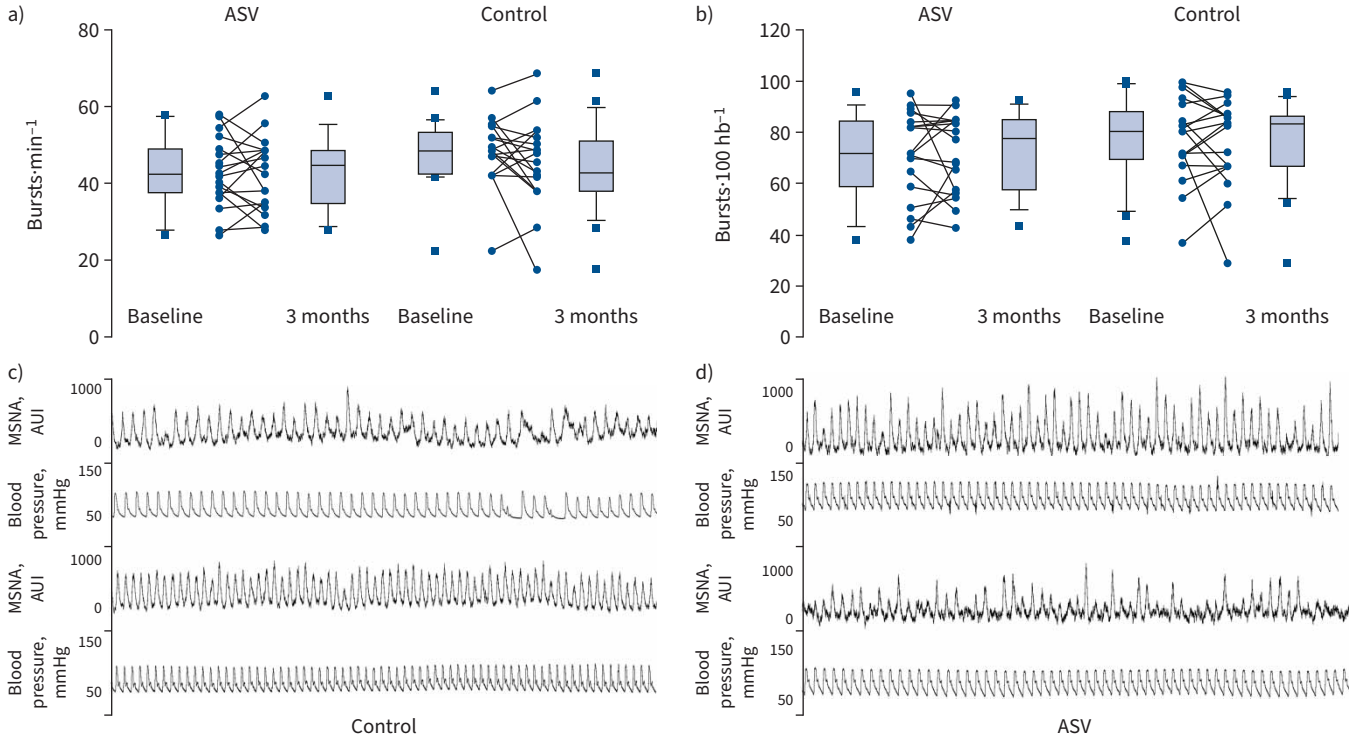

FIGURE 2 a, b) Change in sympathetic tone measured using muscle sympathetic nerve activity (MSNA) expressed both in a) bursts per minute (bursts·min^{-1}) and b) bursts per 100 heart beats (bursts·100 hb^{-1}). c, d) Sample MSNA and blood pressure raw signals from two patients: c) control and d) adaptive servo-ventilation (ASV). AUI: arbitrary integration units.

TABLE 4 Secondary end-point variables at baseline (n=40) and follow-up (n=39)

	Baseline	3 months	Difference	p-value		
				Group	Time	Interaction
Weight, kg				0.61	0.97	0.40
Control	80.1±14.8	79.5±13.5	−0.7±6.2			
ASV	77.0±16.4	77.7±16.4	0.7±3.2			
6MWT, % pred[#]				0.91	**0.02**	0.21
Control	81.6±21.0	89.1±18.1	7.5±13.5			
ASV	84.7±14.6	87.1±12.5	2.4±11.5			
6MWT, m				0.11	0.36	0.64
Control	367.9±91.8	390.6±115.5	17.3±90.6			
ASV	431.9±104.1	431.2±122.6	8.5±69.9			
MLHFQ score				0.99	0.05	0.35
Control	22.0±14.2	19.4±14.1	−2.6±17.7			
ASV	24.5±15.7	17.0±13.0	−7.6±14.3			
ESS score[#]				0.23	0.84	0.76
Control	5.5 (4–8.5)	4 (4–6)	0 (–2–1.5)			
ASV	5 (3–9)	5 (2–5)	0 (–3–2)			
RR interval, s[#]				0.65	0.11	0.57
Control	966.5±152.4	1014.3±109.8	47.7±124.3			
ASV	993.9±123.8	1016.7±88.7	22.8±146.6			
SBP, mmHg[#]				0.60	**0.04**	0.30
Control	125.9±22.1	114.5±16.2	–11.4±20.8			
ASV	119.5±23.1	115.5±15.3	–3.9±23.8			
DBP, mmHg[#]				0.17	0.54	0.24
Control	70.6±13.2	69.6±9.9	–1.1±12. 8			
ASV	64.7±9.8	68.0±7.1	3.4±10.3			
ABF, cm·s^{-1}[#]				0.94	**0.02**	0.62
Control	3.6 (3.0–3.8)	4.0 (3.5–4.7)	0.3 (–0.1–1.0)			
ASV	3.7 (3.1–4.3)	4.2 (3.7–4.5)	0.4 (–0.1–1.1)			
Plasma haemoglobin, g·dL^{-1}				0.66	0.50	0.16
Control	13.9±1.6	13.5±1.7	–0.4±1.4			
ASV	13.5±1.1	13.6±1.3	0.1±0.7			
Plasma creatinine, µmol·L^{-1}				0.78	0.57	0.74
Control	122.0±33.6	118.7±27.5	–3.3±25.7			
ASV	123.1±31.0	122.2±30.8	–0.9±18.8			
24-h urinary catecholamines, nmol·mmol^{-1} creatinine[#]						
Noradrenaline				0.44	0.50	0.97
Control	17.4 (11.9–28.3)	14.1 (11.3–26.3)	0 (–2.1–3.7)			
ASV	18.7 (16.8–24.1)	17.9 (13.1–23.2)	0 (–1.3–0)			
Adrenaline				0.87	0.37	0.73
Control	2.3±1.3	2.1±1.2	–0.2±1.4			
ASV	2.3±1.4	1.9±1.3	–0.4±1.1			
Dopamine				0.45	0.13	0.89
Control	72.6±45.5	66.1±36.7	–6.5±24.9			
ASV	84.8±28.0	77.0±29.6	–7.8±15.1			

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. ASV: adaptive servo-ventilation; 6MWT: 6-min walk test; MLHFQ: Minnesota Living with Heart Failure Questionnaire; ESS: Epworth Sleepiness Scale; SBP: systolic blood pressure; DBP: diastolic blood pressure; ABF: arterial blood flow (Doppler). [#]: missing values: 6MWT n=2; ESS score n=1; SBP, DBP, RR interval, ABF, 24-h urinary catecholamines n=17. Significance ($p<0.05$) is indicated in bold.

(figure 3c). In the control group, a decrease in sympathetic activity was associated with lower cardiovascular mortality; however, 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 (supplementary tables S1–S5) and LVEF subgroup (supplementary tables S6–S8) analyses did not differ markedly from those of the ITT analysis.

TABLE 5 Determinants of sympathetic activity at baseline in all patients

	Bursts·min^{-1}		Bursts·100 hb^{-1}	
	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
β-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**
Natraemia[#]	–0.88 (–1.92–0.16)	0.09	–0.83 (–3.09–1.43)	0.46
ODI	0.13 (0–0.27)	0.06	0.14 (–0.12–0.41)	0.28
Mean S_{pO_2}	–1.09 (–2.74–0.57)	0.19	–2.91 (–5.98–0.15)	0.06

Bursts·min^{-1}: bursts per minute; bursts·100 hb^{-1}: bursts per 100 heart beats; ESS: Epworth Sleepiness Scale; ODI: oxygen desaturation index; S_{pO_2}: oxygen saturation measured by pulse oximetry. [#]: missing values: plasma haemoglobin n=2; natraemia n=8. Significance (p<0.05) is indicated in bold.

Discussion

The SERVE-HF ITT 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 upregulation 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 3 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 end-points. 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 haemodynamic 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

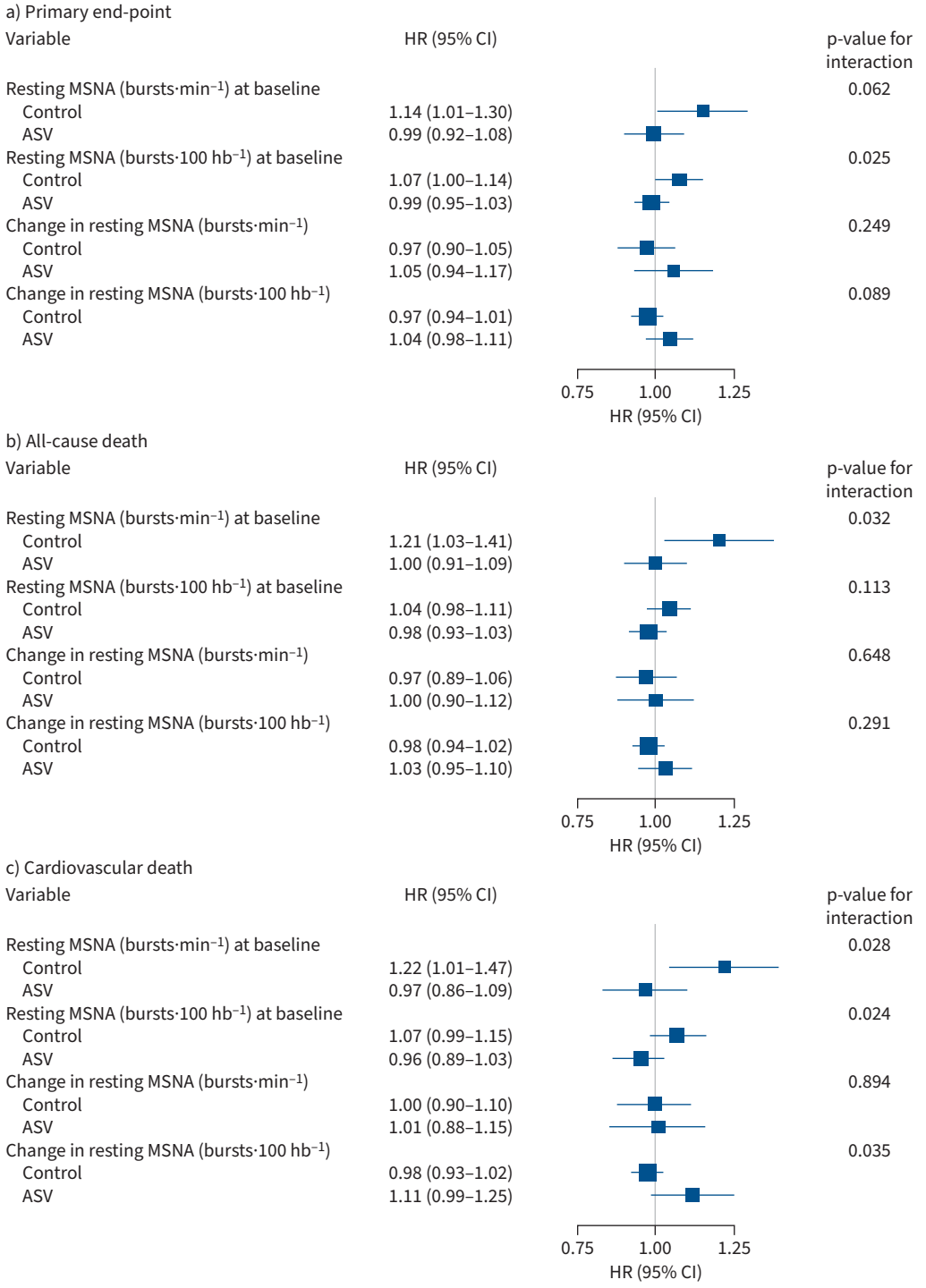

FIGURE 3 Relationship between sympathetic tone measured using muscle sympathetic nerve activity (MSNA) in the control and adaptive servo-ventilation (ASV) groups and risk of: a) primary end-point (all-cause death, or life-saving cardiovascular intervention or unplanned hospitalisation for worsening chronic heart failure): events in seven (33.3%) and seven (36.8%) patients in the control and ASV groups, respectively; b) all-cause death: events in six (28.6%) and five (26.3%) patients in the control and ASV groups, respectively; and c) cardiovascular death: events in five (23.8%) and three (15.8%) patients in the control and ASV groups, respectively. Bursts·min^{-1}: bursts per minute; bursts·100 hb^{-1}: bursts per 100 heart beats. Cox regression with Firth's penalised maximum likelihood bias reduction method was applied. For continuous independent variables, results are presented as hazard ratio (HR) values for a 1-unit increase in the independent variable within the randomisation group. Statistical significance of a difference in those HR values is given as "p-value for interaction".

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 β-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 $kg \cdot m^{-2}$ 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 substudy differed in some respects to the overall SERVE-HF population (supplementary table S9). Body weight was lower in the MSNA cohort although body mass index was

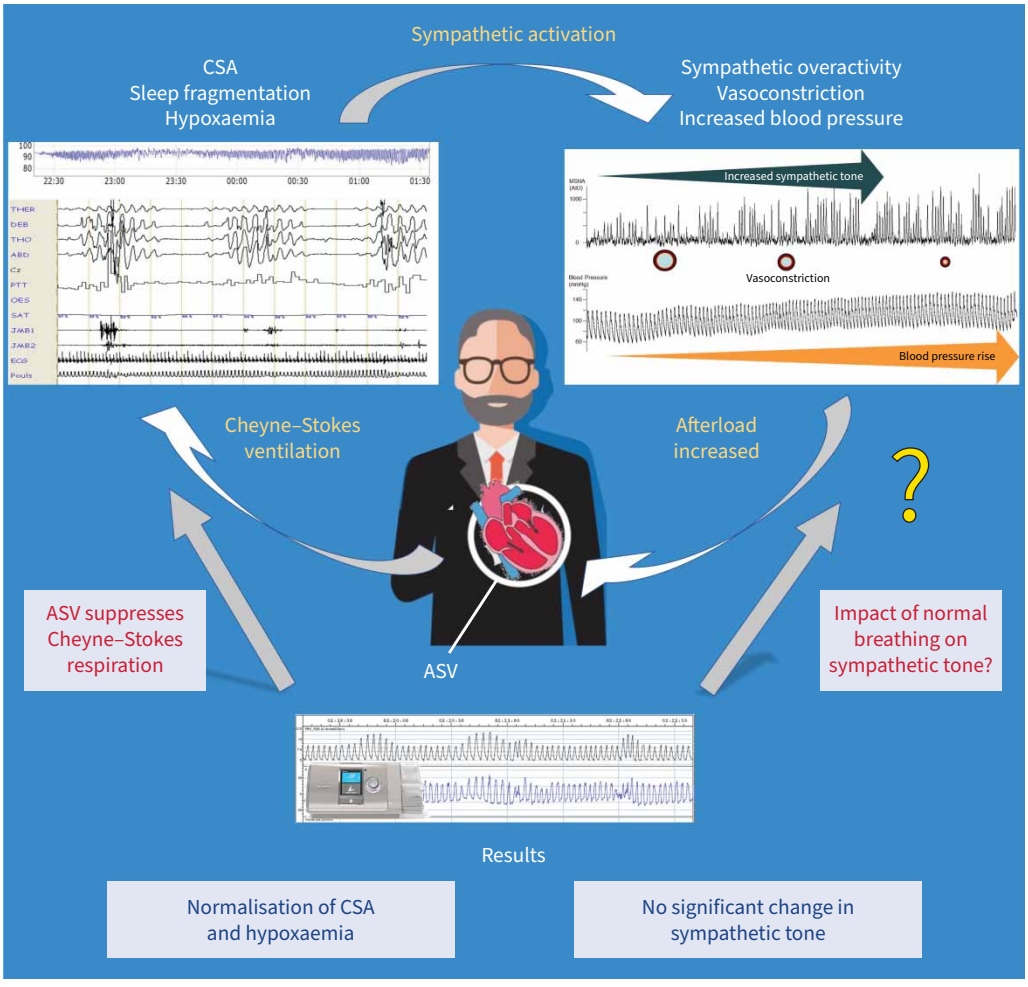

FIGURE 4 Summary figure. In chronic heart failure patients, the suppression of central sleep apnoea (CSA) by adaptive servo-ventilation (ASV) does not have a significant effect on chronic heart failure-related sympathetic activation and leads to increased cardiovascular mortality.

similar. This analysis included more patients in NYHA Functional Class I and with a longer 6MWD. 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 angiotensin converting enzyme 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 (figure 4), 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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