RESEARCH ARTICLE

Effect of adaptive servo ventilation on central sleep apnea and sleep structure in systolic heart failure patients: polysomnography data from the SERVE-HF major sub study

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Summary

This SERVE-HF (Treatment of Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients With Heart Failure) sub study analysis evaluated polysomnography (PSG) data in patients with heart failure with reduced ejection fraction (HFrEF) and predominant central sleep apnea (CSA) randomised to guideline-based medical therapy, with or without adaptive servo ventilation (ASV). Patients underwent full overnight PSG at baseline and at 12 months. All PSG recordings were analysed by a core laboratory. Only data for patients with baseline and 3- or 12-month values were included. The sub study included 312 patients; the number with available PSG data differed for each variable (94–103 in the control group, 77–99 in the ASV group). After 12 months, baseline-adjusted respiratory measures were significantly better in the ASV group versus control. Although some between-group differences in sleep measures were seen at 12 months (e.g., better sleep efficiency in the ASV group), these were unlikely to be clinically significant. The number of periodic leg

movements during sleep (PLMS) increased in the ASV group ($p = 0.039$). At 12 months, the respiratory arousal index was significantly lower in the ASV versus control group ($p < 0.001$), whilst the PLMS-related arousal index was significantly higher in the ASV group ($p = 0.04$ versus control). ASV attenuated the respiratory variables characterising sleep apnea in patients with HFrEF and predominant CSA in SERVE-HF. Sleep quality improvements during ASV therapy were small and unlikely to be clinically significant. The increase in PLMS and PLMS-related arousals during ASV warrants further investigation, particularly relating to their potential association with increased cardiovascular risk.

KEYWORDS
adaptive servo ventilation, central sleep apnea, periodic leg movements during sleep, polysomnography, systolic heart failure

INTRODUCTION

Central sleep apnea (CSA) and Cheyne–Stokes respiration (CSR) are common sleep-disordered breathing (SDB) patterns in patients with heart failure (HF) (Levy et al., 2007). Prevalence rates range from 25% to 40% (Levy et al., 2007) and increase in parallel with HF severity (Oldenburg et al., 2007). Several studies have reported an independent association between the presence of CSA and increased morbidity and mortality in patients with HF (Bitter et al., 2011; Yumino et al., 2009). This elevated risk appears to persist even during optimally titrated medical therapy for HF (Bitter et al., 2011; Oldenburg et al., 2011).

Studies investigating the effects of positive airway pressure (PAP) on CSA/CSR have reported conflicting results, with some showing beneficial effects while others have not (Arzt et al., 2013; Bradley et al., 2005; Naughton et al., 1995; Oldenburg et al., 2008; Pepperell et al., 2003). This may, at least in part, be due to suboptimal improvements in SDB during treatment, secondary to inadequate titration and/or poor device usage.

Another aspect that must be considered is an incomplete normalisation of sleep macro- and microstructure. For example, treatment of CSA with continuous PAP (CPAP) does not reduce arousal frequency in patients with HF (Ruttanaumpawan et al., 2009). The absence of improvement in sleep quality with automatically titrating CPAP (APAP) has been suggested as an explanation for increases in sympatho-vagal tone (Spiesshoefer et al., 2019). Indeed, as in the general population, both short and long sleep duration were associated with cardiovascular morbidity and mortality. More precisely, given that long sleep duration in chronic HF is associated with poor sleep quality (Reinhard et al., 2013), objective short sleep duration and objective bad sleep quality are the two factors that appear to be associated with poor prognosis and cardiovascular morbidity/mortality risk (Hetzenecker, Escourrou, et al., 2016). Interestingly, in patients with HF with reduced ejection fraction (HFrEF), poor sleep quality associated with a periodic limb movement index (PLMI) of >5 has been linked with increased mortality risk (Yumino et al., 2011).

Although there is no established a cause–effect relationship between poor sleep quality and mortality, improvements in ventilation during adaptive servo ventilation (ASV) therapy in patients with HF and severe CSA or OSA should also be associated with an improvement in sleep quality that could have a positive impact on mortality. Current data on the effects of ASV on sleep fragmentation and sleep quality are limited and this topic merits further investigation (Hetzenecker, Escourrou, et al., 2016).

In the Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) study, control of CSA/CSR (based on the apnea–hypopnea index [AHI]) was not associated with improved clinical outcomes (Cowie et al., 2015). Indeed, patients randomised to ASV had higher rates of cardiovascular mortality compared with those allocated to the control group (Cowie et al., 2015). A pre-planned sub study of SERVE-HF evaluated polysomnography (PSG) data in the SERVE-HF sub study population to provide insights into the mechanistic effects of ASV in HFrEF. This ore analysis attempt to determine the effects of ASV on central sleep apnea and sleep structure in patients with HFrEF.

METHODS

Study population

A total of 29 of 91 SERVE-HF study centres contributed patients to the major sub study (Cowie et al., 2018). These centres were selected based on their ability to perform full PSG (diagnostic and on ASV with pneumotachograph), their ability to comply with the centre selection process for the major sub study, and the ability to format PSG data into European data format (EDF). Full details of the SERVE-HF study inclusion and exclusion criteria (Cowie et al., 2013; Cowie et al., 2015), and the sub study design (Cowie et al., 2018), have been reported previously. In brief, eligible patients were aged ≥22 years and had symptomatic chronic HF (New York Heart Association

[NYHA] class III or IV, or class II with ≥1 HF-related hospitalisation in the previous 24 months) and reduced left ventricular ejection fraction (LVEF ≤45%) (Ponikowski et al., 2016). All patients were being treated with stable, guideline-based medical therapies for HF. SDB inclusion criteria (based on PSG data recorded within 4 weeks of randomisation) were the presence of predominant CSA (AHI ≥15 events/h, >50% central events, central AHI ≥10 events/h).

The SERVE-HF sub study protocol was approved by the appropriate local or regional ethics committees at each study centre/region. The trial was conducted according to Good Clinical Practice and the Principles of the Declaration of Helsinki 2002. All participants gave written informed consent.

Study intervention

In SERVE-HF, patients were randomised to receive optimal medical therapy for HF (Ponikowski et al., 2016) alone, or in combination with ASV (Auto Set CS, ResMed). Full details of ASV titration and settings have been reported previously (Cowie et al., 2015).

Assessments

Patients underwent full overnight PSG at baseline and again at the 12-month follow-up. PSG included electroencephalogram (EEG), electro-oculogram, electromyogram and electrocardiogram channels. Nasal airflow was measured using a nasal cannula connected to a pressure transducer, oral airflow was measured using a mouth thermistor, abdominal and thoracic effort was determined using respiratory inductance plethysmography, piezo-sensors or pneumo-bands, oximetry was used to determine oxygen saturation. For the 3- and 12-month PSG, airflow was measured using a pneumotachograph and mask pressure was determined on a different channel from the pneumotachograph. Although monitored in all PSG studies, body position data were not available in EDF files due to the EDF transformation process. Therefore, body position was not considered in the analysis.

All PSG data were scored centrally in a blinded manner by a core laboratory (Grenoble, France) using standard criteria (Berry et al., 2012). All scoring was performed manually by at least two scorers, with discrepancies resolved by adjudication of a third (senior) scorer. The senior scorer also reviewed a random selection of recordings in their entirety.

Apnea was defined as complete cessation of airflow for ≥10 s. Hypopnea was defined as a ≥50% reduction in the nasal pressure signal or a 30%–50% decrease associated with either oxygen desaturation (≥3%) or EEG arousal, both lasting for ≥10 s. Apneas were classified as obstructive, central, or mixed according to the presence or absence of respiratory efforts. Mixed apneas were defined by absence of respiratory efforts at the beginning of an apnea followed by three or more respiratory efforts without detectable flow at their end. Hypopneas were classified as obstructive or central based on the presence or absence of respiratory efforts plus the

shape of the respiratory curve of nasal pressure (e.g., flow limitation) (Randerath et al., 2013). The AHI was calculated as the number of apneas and hypopneas per hour of sleep time. The percentage of central events was calculated and defined as the ratio of all central events (apneas and hypopneas) to all disordered breathing events. The respiratory disturbance index (RDI) was calculated as the number of apneas, hypopneas and flow limitation respiratory events per hour of sleep time, and the oxygen desaturation index (ODI) was determined as number of oxygen desaturations (≥3%) during sleep.

Endpoints

Sleep measures, including changes in sleep duration and sleep stages, were secondary endpoints in the SERVE-HF sub study. The primary sub study endpoint was change in LVEF from baseline to 12 months (Cowie et al., 2018).

Statistical analysis

This study is a sub analysis of the main SERVE-HF sub study and was not initially powered for sleep outcomes analysis. All analyses were conducted in the intention-to-treat (ITT) population (all sub study ITT patients with available data at baseline and 12 months) and the per-protocol (PP) population (all sub study ITT patients maintaining their randomised therapy at least until 12 months).

Continuous variables are reported as means and standard deviations (SDs) and categorical variables are presented as frequencies and percentages. For analyses of changes in sleep and breathing measures between baseline, 3- and 12-months' follow-ups, separate analysis of covariance (ANCOVA) models for the 3- and 12-month scores were applied to independently assess the short- and long-term effect of ASV therapy. Each model was adjusted for baseline values of the parameter being investigated in that model; in case of excessive zeros, a baseline zero-indicator was included for further adjustment. Where appropriate, continuous outcomes were log-transformed before analysis. As an important high-risk subgroup, patients with severely impaired LVEF (<30%) were studied by including an interaction term between treatment and an indicator for LVEF <30% in the respective ANCOVA models. A two-tailed $p < 0.05$ was defined as statistically significant. All analyses were conducted using STATA 14.2 (STATA Corporation).

RESULTS

Study population

The SERVE-HF sub study included 312 patients from SERVE-HF centres in Germany (recruiting 246 patients), France (16), Finland (seven), UK (three), Australia (29), Czech Republic (seven), Switzerland (three)

TABLE 1 Baseline demographic and clinical characteristics of patients enrolled in the SERVE-HF sub study

Characteristic	Control (n = 153)	ASV (n = 159)
Age, years, mean (SD)	69.1 (10.3)	69.5 (9.7)
Male, n (%)	139/153 (90.8)	144/159 (90.6)
Body mass index, kg/m², mean (SD)	29.4 (5.0)	28.9 (4.7)
NYHA class, n (%)		
II	36/152 (23.7)	46/158 (28.9)
III	116/152 (76.3)	112/158 (70.4)
LVEF, %, mean (SD)	33.8 (8.1)	32.2 (8.3)
Diabetes mellitus, n (%)	68/152 (44.7)	68/158 (43.0)
Ischaemic HF, n (%)[a]	89/152 (58.6)	89/156 (56.0)
Sinus rhythm, n (%)	83/151 (55.0)	85/158 (53.8)
Implanted device, n (%)	88/153 (57.5)	99 (62.3)
Estimated GFR, mL/min/1.73 m², mean (SD)	59.0 (22.6)	59.1 (20.3)
6-min walk distance, m, mean (SD)	343.9 (123.1)	339.7 (120.0)
Cardiac medication, n (%)		
ACEI or ARB	147/153 (96.1)	144/159 (90.6)
β-blocker	144/153 (94.1)	140/159 (88.1)
Aldosterone antagonist	86/153 (56.2)	96/159 (60.4)
Diuretic	134/153 (87.6)	129/159 (81.1)
Cardiac glycoside	28/153 (18.3)	38/159 (23.9)
Anti-arrhythmics	19/153 (12.4)	24/159 (15.1)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASV, adaptive servo ventilation; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter–defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Values are mean (± standard deviation [SD]), or number of patients (percentage of patients with data available).

and the Netherlands (one). The ASV and control groups had similar characteristics at baseline (Table 1). The number of patients with PSG data available at baseline were 300, 153 and 147 for the intervention and control group, respectively. Therefore, data available for analysis in each follow-up (3 and 12 months) visit differed for each variable: from 94–103 in the control group and 77–99 in the ASV group in the ITT population (Figure S1).

Respiratory measures

In the ITT analysis, all baseline-adjusted respiratory parameters at the 3- and 12-month follow-up were significantly better in the ASV versus control group (Table 2). Similar results were obtained in the PP analysis (Table S1). No group-specific treatment effects were found for patients with LVEF <30% versus ≥30%.

Sleep measures

The ITT analysis showed some statistically significant differences between the ASV and control groups at 12 months, including better sleep efficiency in the ASV group (Table 3). However, differences were numerically small and were not considered to be clinically significant. Again, the results of the PP analysis were consistent with those of the ITT analysis (Table S2).

The respiratory arousal index was significantly lower in the ASV versus control group at 12 months (ITT: 5.4 versus 13.1 events/h; $p < 0.001$); this was partially offset by a trend towards a higher periodic leg movements during sleep (PLMS)-related arousal index in the ASV group (3.7 versus 2.0 events/h; $p = 0.04$) (Figure 1, Table 3). Findings were similar in the PP analysis, but the between-group difference in PLMS-related arousals achieved statistical significance (Table S2). The 12-month respiratory arousal index was 4.4 events/h in the ASV group compared with 15.2 events/h in the control group ($p < 0.001$); corresponding values for PLMS-related arousals were 3.6 and 1.6 events/h ($p = 0.019$). Again, no subgroup-specific treatment effects were found for patients with severely reduced LVEF. Although values were similar at baseline, the PLMS index increased markedly in the first 3 months after initiation of ASV and was significantly higher in the ASV versus control group at 12 months (ITT: $p = 0.039$) (Figure 2, Table 3); results were similar in the PP analysis (data not shown).

Compared with 12 months, the 3-month statistical analysis did not find improvement in sleep efficiency or decrease in sleep latency, but there was a decrease in Stage 1 sleep duration. There was no other difference in the analysis for the ITT population at the 3- and 12-month follow-ups compared with baseline.

DISCUSSION

The SERVE-HF major sub study PSG data confirm the ability of ASV to control SDB in patients with HFrEF. However, the residual AHI based on PSG data in this analysis (mean [SD] 12.1 [14.5] events/h of total sleep time [TST]) cannot be classified as effective or optimal control, which should be an AHI of at least <10 events/h. The findings also suggest that the small improvements in sleep quality during ASV therapy are unlikely to be clinically significant, which could contribute to the unchanged quality of life reported in the main SERVE-HF analysis (Cowie et al., 2015). A substantial reduction in SDB, particularly central events, in the ASV group is consistent with existing literature showing that ASV is a successful method for treating CSA/CSR in HF (Fietze et al., 2008; Philippe et al., 2006; Teschler et al., 2001).

The increase in PLMS and PLMS-related arousals over time, particularly in the ASV group, is an interesting finding. There are currently few data on the interplay between PLMS, ASV and HF evolution (Xie et al., 2019). PLMS are particularly prevalent in those with lower LVEF and higher NYHA class (Hanly & Zuberi-Khokhar, 1996; Skomro et al., 2009; Yumino et al., 2011). In addition, PLMS has been reported as a predictor of all-cause and cardiac mortality in patients with HF

TABLE 2 Respiratory variables in the intention-to-treat analysis

Variable, mean (SD)	Control			ASV			p 3-month comparison		p 12-month comparison	
	Baseline	3 months	12 months	Baseline	3 months	12 months	Group difference	Interaction[a]	Group difference	Interaction[a]
AHI, event/h	42.7 (18.5) (n = 121)	38.2 (20.2) (n = 111)	33.9 (19.7) (n = 97)	43.6 (18.8) (n = 125)	11.1 (13.9) (n = 113)	12.1 (14.5) (n = 92)	<0.001	0.718	<0.001	0.218
cAI, events/h	18.7 (17.7) (n = 121)	15.5 (17.4) (n = 111)	11.8 (15.8) (n = 97)	17.7 (18.9) (n = 128)	2.2 (6.5) (n = 115)	2.8 (7.9) (n = 93)	<0.001	0.872	<0.001	0.145
oAI, events/h	2.0 (4.9) (n = 121)	2.5 (6.3) (n = 111)	2.1 (5.8) (n = 97)	2.9 (6.2) (n = 128)	0.8 (4.3) (n = 115)	0.5 (2.1) (n = 93)	<0.001	0.559	<0.001	0.786
Mixed AI, events/h	1.1 (3.4) (n = 121)	0.9 (3.5) (n = 111)	0.7 (2.4) (n = 97)	2.0 (6.2) (n = 128)	0.2 (1.6) (n = 115)	0.3 (1.4) (n = 93)	<0.001	0.072	<0.001	0.294
cAHI/AHI, %	72.0 (27.9) (n = 119)	63.5 (32.8) (n = 109)	59.6 (34.8) (n = 94)	67.9 (28.5) (n = 115)	43.0 (35.4) (n = 97)	37.7 (35.5) (n = 77)	<0.001	0.975	<0.001	0.772
Time with CSR, % of TST	56.9 (49.0) (n = 121)	44.6 (46.7) (n = 111)	35.0 (42.0) (n = 97)	48.0 (46.3) (n = 125)	6.0 (20.5) (n = 112)	7.4 (19.4) (n = 92)	<0.001	0.510	<0.001	0.621
RDI, events/h	42.7 (18.5) (n = 121)	38.2 (20.2) (n = 111)	34.0 (19.6) (n = 97)	43.7 (18.8) (n = 125)	11.1 (13.9) (n = 113)	12.1 (14.5) (n = 92)	<0.001	0.723	<0.001	0.206
ODI, events/h	37.1 (18.9) (n = 116)	32.9 (19.2) (n = 105)	29.3 (17.7) (n = 96)	37.8 (17.3) (n = 130)	11.4 (12.5) (n = 117)	13.5 (13.6) (n = 93)	<0.001	0.589	<0.001	0.638
Mean SpO$_2$, %	92.9 (2.2) (n = 116)	93.3 (2.0) (n = 104)	93.1 (1.9) (n = 96)	92.6 (2.3) (n = 129)	93.7 (1.7) (n = 116)	93.7 (1.8) (n = 92)	0.043	0.776	0.001	0.255
Time with SpO$_2$ < 90%	43.8 (59.3) (n = 116)	38.7 (54.6) (n = 105)	35.5 (49.4) (n = 96)	50.5 (59.3) (n = 129)	18.8 (40.3) (n = 116)	19.9 (41.2) (n = 92)	<0.001	0.359	<0.001	0.236

AHI, apnea–hypopnea index; AI, apnea index; ASV, adaptive servo ventilation; cAHI, central apnea–hypopnea index; cAI, central apnea index; CSR, Cheyne–Stokes respiration; oAI, obstructive apnea index; ODI, oxygen desaturation index; RDI, respiratory disturbance index; SpO$_2$ capillary oxygen saturation; TST, total sleep time.

Values are mean (± standard deviation [SD]). Numbers in brackets indicate the number of patients (at baseline this is the number of patients with measurement at baseline and at least one of the two follow-up visits; at 3 and 12 months this is the number of patients with data available at that time point).

[a]Test for different treatment effects at 3 or 12 months in patients with severely impaired left ventricular ejection fraction (LVEF; <30%) versus patients with moderately impaired LVEF (≥30%).

TABLE 3 Sleep variables in the intention-to-treat analysis

Variable, mean (SD)	Control			ASV			p 3-month comparison		p 12-month comparison	
	Baseline	3 months	12 months	Baseline	3 months	12 months	Group difference	Interaction[a]	Group difference	Interaction[a]
TST, min	296.3 (75.8) (n = 122)	296.1 (84.0) (n = 114)	282.0 (84.8) (n = 103)	302.4 (74.8) (n = 135)	288.9 (76.5) (n = 126)	299.8 (71.7) (n = 99)	0.588	0.829	0.195	0.340
WASO, min	122.8 (69.1) (n = 122)	123.1 (69.0) (n = 114)	131.4 (68.0) (n = 103)	119.6 (69.2) (n = 135)	121.1 (66.6) (n = 126)	111.7 (68.0) (n = 99)	0.648	0.052	0.080	0.811
Sleep efficiency, %	66.1 (15.6) (n = 122)	65.7 (16.1) (n = 114)	62.6 (17.3) (n = 103)	67.0 (14.9) (n = 135)	66.3 (14.9) (n = 126)	68.8 (14.9) (n = 99)	0.432	0.544	0.013	0.930
Sleep latency, min:										
Stage 1	34.3 (28.1) (n = 122)	36.4 (37.6) (n = 114)	43.8 (36.0) (n = 103)	32.4 (22.9) (n = 135)	35.9 (39.6) (n = 126)	31.1 (36.2) (n = 99)	0.157	0.834	0.006	0.098
Sleep duration, min:										
Stage 1	73.3 (43.8) (n = 122)	70.2 (47.2) (n = 114)	70.3 (44.6) (n = 103)	72.8 (45.8) (n = 135)	52.2 (37.2) (n = 126)	59.5 (40.0) (n = 99)	0.037	0.713	0.077	0.908
Stage 2	158.6 (77.2) (n = 122)	154.0 (68.8) (n = 114)	143.4 (63.1) (n = 103)	159.7 (69.8) (n = 135)	161.0 (62.8) (n = 126)	158.2 (64.5) (n = 99)	0.650	0.419	0.114	0.179
Stage 3 + 4	18.2 (30.9) (n = 122)	20.3 (38.7) (n = 114)	17.0 (31.5) (n = 103)	17.5 (31.4) (n = 135)	16.9 (30.9) (n = 126)	21.5 (34.3) (n = 99)	0.401	0.892	0.098	0.655
REM	46.1 (27.3) (n = 122)	51.5 (33.9) (n = 114)	51.3 (29.9) (n = 103)	52.4 (29.1) (n = 135)	58.8 (29.5) (n = 126)	60.6 (30.0) (n = 99)	0.283	0.390	0.110	0.318
PLMS, events/h	12.1 (28.5) (n = 122)	15.9 (30.1) (n = 113)	19.5 (46.1) (n = 103)	14.9 (25.2) (n = 134)	31.6 (42.3) (n = 125)	33.5 (50.6) (n = 98)	<0.001	0.554	0.039	0.185
RAI, events/h	17.6 (11.7) (n = 122)	14.8 (10.6) (n = 113)	13.1 (10.7) (n = 103)	17.8 (11.3) (n = 135)	4.5 (7.1) (n = 126)	5.4 (7.1) (n = 99)	<0.001	0.637	<0.001	0.993
PLMS arousal index, events/h	1.3 (3.5) (n = 122)	1.9 (4.7) (n = 113)	2.0 (4.4) (n = 103)	1.5 (3.5) (n = 135)	3.7 (5.9) (n = 126)	3.7 (6.8) (n = 99)	<0.001	0.875	0.040	0.133
All arousals, events/h	101.9 (56.3) (n = 122)	94.7 (52.7) (n = 113)	83.6 (51.1) (n = 103)	106.8 (64.8) (n = 135)	58.4 (38.1) (n = 126)	63.7 (48.2) (n = 99)	<0.001	0.663	0.041	0.548

ASV, adaptive servo ventilation; PLMS, periodic leg movement during sleep; RAI, respiratory arousal index; REM, rapid eye movement; TST, total sleep time; WASO, wake after sleep onset.

Values are mean (± standard deviation [SD]). Numbers in brackets indicate the number of patients (at baseline this is the number of patients with measurement at baseline and at least one of the two follow-up visits; at 3 and 12 months this is the number of patients with data available at that time point).

aTest for different treatment effects at 3 or 12 months in patients with severely impaired left ventricular ejection fraction (LVEF; <30%) versus patients with moderately impaired LVEF (≥30%).
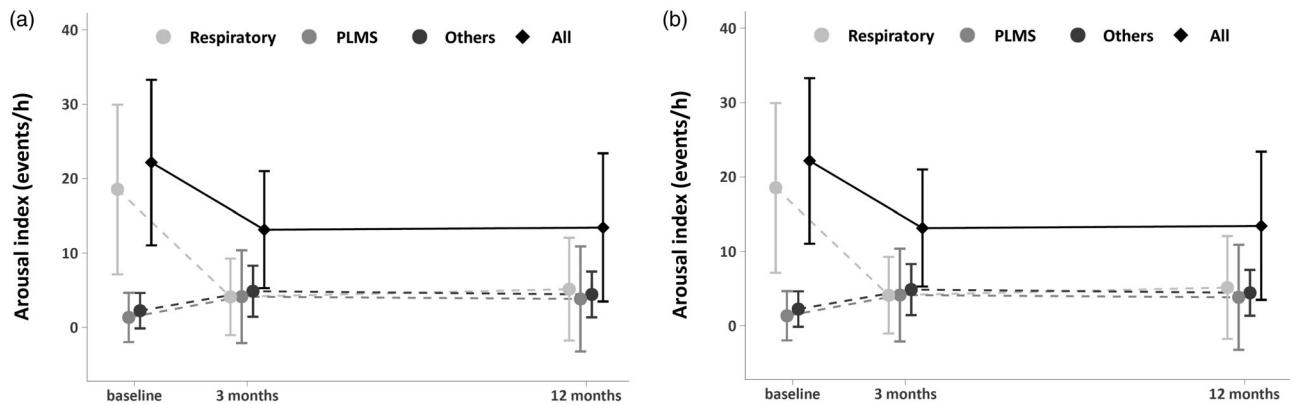
FIGURE 1 Arousal index (events/h) in the control (a) and adaptive servo ventilation (ASV) (b) groups (intention-to-treat analysis)

FIGURE 2 Periodic leg movement during sleep (PLMS) index (events/h) in the control and adaptive servo ventilation (ASV) groups (intention-to-treat analysis)
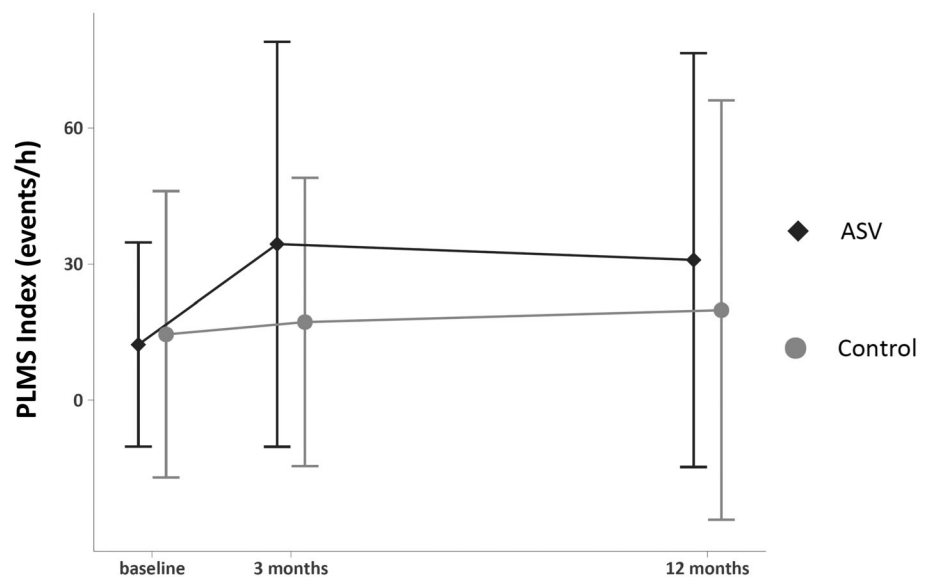
with preserved or reduced LVEF (Yatsu et al., 2017; Yoshihisa et al., 2011; Yumino et al., 2011). The presence of severe PLMS (PLMS index ≥30 events/h) was significantly associated with a higher rate of death and readmission in patients hospitalised for acute decompensation of HF (hazard ratio 2.16, 95% confidence interval 1.03–4.54; $p = 0.042$ versus PLMS index <30 events/h), independently of haemoglobin level and SDB severity (Yatsu et al., 2017). The PLMS index in the ASV group in this SERVE-HF sub study analysis can be categorised as "severe" and could therefore be one potential mechanism contributing to the increased cardiovascular mortality seen in SERVE-HF study participants randomised to the ASV group.

There are some potential mechanisms by which PLMS could have an adverse impact on the cardiovascular system. PLMS in OSA have been associated with an increase in sympathetic nervous system activity versus OSA alone.

In addition, causality cannot be determined based on available data. However, PSG findings from the SERVE-HF sub study indicate the possibility that an increase in PLMS (possibly representing an increase in sympathetic nervous system activity) could potentially be

one factor contributing to the higher mortality reported in patients randomised to ASV in the main SERVE-HF trial, especially because the proportion of patients with atrial fibrillation at baseline was significantly higher in the ASV versus control group (Cowie et al., 2015).

Another possibility, which is the most likely mechanism, is that treatment of SDB during ASV therapy unmasks existing PLMS. Using current criteria (Berry et al., 2012), any limb movements occurring from 0.5 s before to 0.5 s after a respiratory event are not scored as PLMS. Therefore, fewer respiratory events during ASV therapy could result in detection of more PLMS events without a meaningful increase in the actual number of events overall. A significant increase in the number of PLMS events has been reported during titration of CPAP therapy in adults and children with OSA and was described as "unmasking" of PLMS associated with respiratory events and arousals (Baran et al., 2003; Hedli et al., 2012). An increase in PLMS with arousals has also been documented during titration of oral appliance therapy in patients with OSA (Guerrero et al., 2010).

In the main SERVE-HF study population, ASV reduced the AHI from a mean (SD) of 31.2 (12.70 events/h (based on polygraphy or

PSG) to 6.6 events/h at 12 months (reported from ASV devices) (Cowie et al., 2015). However, based on PSG data (TST) in a subset of patients, the AHI in this analysis decreased from a mean (SD) of 42.8 (17.8) events/h at baseline to 12.1 (14.5) events/h at 12 months. The AHI based on PSG scoring in the present study may have been stricter than the data retrieved from ASV devices, resulting in higher AHI values. Nevertheless, the present findings highlight the challenges of effectively controlling CSA with a target AHI of <10 events/h or <5 events/h during ASV therapy in patients with systolic HF. According to the European Respiratory Society (ERS) taskforce, the recommendation for sufficient reduction of AHI in patients with CSA was proposed as <15 events/h (Randerath et al., 2017). The differences between AHI values based on PSG data in the subset of patients participating in the SERVE-HF sub study and the overall findings of the main study might also reflect difficulties in maintaining a consistently high standard of care across a large number of different centres.

Although some statistically significant changes in sleep measures were found in this SERVE-HF sub study analysis, these were considered unlikely to be clinically relevant. Normalisation of sleep structure is one goal of treatment in patients with sleep apnea (Spiesshoefer et al., 2019). In the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) study, arousal frequency was still high even when CSA was treated by CPAP (Ruttanaumpawan et al., 2009). This highlights the need to better understand the origin of sleep impairment in patients with HF. Furthermore, it seems important that any proposed pressure support treatment is highly effective in improving sleep. Data from a retrospective analysis indicated that patients with chronic HF whose CSA was not controlled on CPAP had a significant improvement in several measures of sleep quality (e.g., arousal index, time spent in rapid eye movement [REM] sleep) after switching to ASV (Hetzenecker, Roth, et al., 2016). Early studies of ASV in patients with HF with CSA/CSR also suggested that this approach improved sleep quality better than other treatment modalities (Teschler et al., 2001). In prospective non-randomised studies, a significant improvement in sleep quality was seen during treatment with ASV (Roder et al., 2020; Turoff et al., 2017), contrasting with the findings of the present analysis.

This analysis is part of a prespecified sub study of a larger trial, and the number of patients with data available at both baseline and follow-up who were therefore included in the present analyses was modest. Furthermore, the sub study was only powered to detect between-group differences in LVEF, and non-survivors, withdrawals and patients lost to follow-up could not contribute to the analysis, limiting the generalisability of the results. Thus, the present findings need to be interpreted with caution.

The results of the PSG analysis in the SERVE-HF sub study population confirm that the respiratory aspects of sleep apnea were reduced by ASV in patients with HFrEF and predominant CSA. Improvements in sleep quality during ASV therapy were small and unlikely to be clinically significant. The lack of any important change in sleep quality could be one reason why quality of life, functional outcomes and sympathetic activity remained unchanged during ASV therapy in SERVE-HF. The potential role of PLMS and PLMS-related arousals for defining a phenotype of patients with HFrEF with SDB who have a worse prognosis warrants further investigation.

AUTHOR CONTRIBUTIONS

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.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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