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Sleep duration and architecture during ASV for central sleep apnoea in systolic heart failure

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ABSTRACT

Background: Adaptive servoventilation (ASV) effectively treats nocturnal respiratory events in patients with heart failure and reduced ejection fraction (HFrEF) and central sleep apnoea (CSA), but increased mortality has been reported. This study investigated changes in sleep architecture during ASV treatment in HFrEF patients.
Methods: A retrospective analysis of polysomnographic datasets for 30 ASV-treated patients with stable HFrEF and moderate-to-severe CSA was performed, including blinded analyses of total sleep time (TST), and percentage of REM and non-REM sleep (stages N1-N3).
Results: Follow-up was 109 ± 32 days; mean device usage was 6.0 ± 1.1 h/day. During ASV there was reduction of N1 (34 ± 20%/TST to 13 ± 5%/TST, $p < 0.001$) and N3 sleep (4 ± 6%/TST to 1 ± 4%/TST, $p = 0.020$), and increase of N2 (44 ± 14%/TST to 62 ± 7%/TST, $p < 0.001$) and REM-sleep (18 ± 8%/TST to 24 ± 6%/TST, $p = 0.002$).
Conclusions: Disturbances of sympatho-vagal balance during ASV might help explain increased mortality during ASV. Since sympathetic tone is highest in REM-sleep and vagal predominance occurs during N3 sleep, these findings generate new hypotheses for the increased mortality seen in SERVE-HF.

1. Background

Disturbed sleep architecture and reduced sleep duration is associated with cardiovascular mortality, reduced quality of life and impaired cognitive function (da Silva et al., 2016; Yang et al., 2015). Sleep-disordered breathing (SDB) is one of the most important factors disrupting sleep architecture, is highly prevalent in heart failure (HF) patients, and is the comorbidity most likely to impair sleep and quality of life due to sleep fragmentation caused by nocturnal disordered breathing events (Punjabi, 2008; Arzt et al., 2016).

In principle, SDB is classified into two main types: obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). With a prevalence of about 20%, OSA is the most frequent SDB subtype in the general population (Young et al., 2002). The main pathophysiological mechanism of OSA is futile respiratory efforts against collapsed upper airways. As cardiac function deteriorates, the prevalence of SDB increases markedly (Punjabi, 2008; Heinzer et al., 2015; Oldenburg et al., 2007). More than 50% of clinically stable HF patients with reduced left ventricular ejection fraction (HFrEF) present with moderate to severe SDB (Oldenburg et al., 2007). In particular, the proportion of central SDB increases as HF progresses, often manifesting as a periodic breathing pattern, classified as Hunter-Cheyne-Stokes respiration (CSR) (Oldenburg et al., 2007; Oldenburg, 2012). These breathing patterns can show long cyclic respiratory events (Oldenburg, 2012; Linz et al., 2011; Narkiewicz et al., 1999) resulting in phases of hypercapnia followed by arousals (Narkiewicz et al., 1999). The main mechanism is an increase in respiratory gain, leading to hyperventilation interrupted by repetitive sleep apnoeas (Türoff et al., 2017; Somers et al., 1989).

CSA has been shown to be associated with worse sleep quality and efficiency compared with OSA (Türoff et al., 2017). The repetitive desaturations and hypercapnia that characterise CSA-CSR activate peripheral and central chemoreceptors, stimulating autonomic reflex responses (Tamisier et al., 2004) leading to impaired sleep architecture and potentially increased sympathetic nerve activity (SNA) (Somers

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et al., 1989). The effects of CSA on sleep architecture have been poorly studied to date, but may provide a mechanistic explanation for the increase in SNA observed in HF patients with CSA, possibly predisposing to cardiac dysrhythmias and sudden cardiac death, as was suggested to occur in the ASV group of the SERVE-HF study (Cowie et al., 2015).

Adaptive servoventilation (ASV) provides anticyclical pressure ventilation and has been shown to effectively suppress CSA (Oldenburg et al., 2008; Miyata et al., 2012; Szollosi et al., 2006; Oldenburg et al., 2018). However, although trials on ASV efficacy are ongoing, one large multicentre randomised controlled trial, the SERVE-HF study (Cowie et al., 2015), reported an increase in all-cause and cardiovascular mortality in HFrEF patients with predominant CSA allocated to ASV. Furthermore, there was also no improvement in quality of life (Minnesota Living with Heart Failure questionnaire, EQ-5D, NYHA classification) or exercise capacity (6-minute walking distance) during the trial (Cowie et al., 2015).

This study (NCT01657188) was designed to investigate potential mechanisms underlying the adverse effects of ASV in patients with HFrEF, and evaluated changes in sleep architecture during treatment.

2. Materials and methods

We performed a retrospective, blinded core-lab analysis of polysomnographic (PSG) recordings at baseline and at follow-up in consecutive stable HFrEF patients with moderate to severe predominant CSA who had ASV treatment initiated after diagnostic PSG. The study protocol was approved by the institutional ethics committee (Reg-no: 43/2013), and all procedures were carried out in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent prior to enrolment in the study.

To facilitate the generalisability of our findings, patient inclusion and exclusion criteria were identical to those used in the SERVE-HF trial (Cowie et al., 2015). In summary, inclusion criteria were: predominant moderate to severe CSA (> 50% central events, apnoea-hypopnoea index [AHI] ≥15/h with a central AHI ≥ 10/h); diagnosis of chronic stable HF (NYHA ≥ II) determined at least 6 months before inclusion; reduced left ventricular ejection fraction (LVEF ≤ 45%) as determined by 2D-echocardiography; and treatment of HF according to current guidelines (Yancy et al., 2013). In addition, to allow meaningful conclusions, our study only included patients with adequate therapy adherence, defined as ASV usage of > 4 h/night on at least 50% of the usage period, and mean application of ≥3 h/night during the last 30 days before follow-up.

Patients with pre-existing SDB therapy (including positive airway pressure therapy, home oxygen therapy, mandibular repositioning devices, and phrenic or hypoglossus nerve stimulation) were excluded. In addition, patients with other sleep disorders (insomnia, parasomnia), manifest depression, acutely decompensated HF, and myocardial infarction, transient ischaemic attack or stroke within the last 3 months were excluded. Additional exclusion criteria were: haemodynamically relevant heart valve diseases (obstructive or regurgitant; grade > 2 on echocardiography or expected to require surgery during the study); significant chronic obstructive pulmonary disease (forced expiratory volume in 1 s < 50%); prior cardiac surgery or percutaneous coronary interventions within the last 6 months; cardiac resynchronization therapy implantation scheduled or performed within 6 months prior to randomization; and untreated restless legs syndrome.

2.1. Data acquisition and analysis

Clinical and laboratory data, comorbidities and medication were collected from routine medical files. We also obtained Epworth Sleepiness Scale (ESS) scores, and electrocardiography (ECG) and echocardiography data. Furthermore, blood gas analysis and routine blood samples, including amino terminal-pro B-type natriuretic peptide (NT-pro-BNP) levels, were collected.

All patients underwent full, in-hospital diagnostic PSG between 2009 and 2013 according to current American Academy of Sleep Medicine (AASM) recommendations, using SOMNOmedics equipment (SOMNOscreen™ and DOMINO™, SOMNOmedics, Randersacker, Germany). Investigations included electroencephalogram, submental electromyogram, electrooculogram, leg movements, body position, activity, ECG and real-time video surveillance. The apnoea-hypopnoea index (AHI) was used as the standard metric for SDB severity. Sleep stages were scored according to the 2012 AASM manual (Berry et al., 2012). The proportion of time spent in each sleep stage was calculated as a percentage of total sleep time (TST). Predominant CSA was defined as > 50% of all events being central apnoeas and/or hypopnoeas in the presence of AHI ≥ 15/h and central AHI (cAHI) > 10/h. PSG analysis was performed in a blinded manner by our partner core laboratory (HP2 Sleep CoreLab, Alpes University, Grenoble, France).

2.2. ASV therapy

ASV was initiated after routine diagnostic PSG using conventional ASV mode. Standard minimum expiratory positive airway pressure (EPAP) was 6 cmH_2O, and inspiratory pressure support was 3 cmH_2O to 15 cmH_2O. Further titration of pressure levels was performed as needed during the initiation night to control obstructive and central events (tailored ASV therapy). After 3 months of ASV treatment, patients were re-admitted to the sleep laboratory for PSG during ASV therapy.

2.3. Statistical analysis

Changes from baseline to follow-up were analysed using *t* test or Wilcoxon's rank sum test for continuous variables and chi-squared test for categorical variables. All tests were performed two-sided, and a *p*-value < 0.05 was considered statistically significant for all comparisons. Statistical analysis was performed using SPSS Software (Version 22, IBM Inc., USA).

3. Results

A total of 30 patients were enrolled in the study (Table 1). The ASV device used was ResMed AutoSet CS/2 in 27 patients, and ResMed AutoSet CS PaceWave in 3 patients. Average minimal EPAP was 6 cmH_2O, minimal inspiratory pressure support was 3 cmH_2O and maximal pressure support was 12 mmH_2O. Therapy interface was full face mask (n = 28) or nasal mask (n = 2), based on patient request. During ASV therapy initiation, the AHI decreased from 45 ± 16/h to 3 ± 3/h.

Follow-up PSG was conducted 109 ± 32 days (median 97 days) after initiation of ASV therapy. ASV was used for at least 4 h/day on 83 ± 14% of study days (median 85%), and mean usage was 6.0 ± 1.1 h/day. Vital signs, clinical parameters and medication use did not change between baseline and follow-up (Table 2).

Respiratory events remained significantly reduced at follow-up (Table 2). Although time spent with oxygen saturation (SpO_2) < 90% significantly decreased during ASV therapy, there were no changes in mean and minimal SpO_2. TST, total sleep period (TSP) and wake after sleep onset time (WASO) were not affected by use of ASV (Table 3). In contrast, time spent in N1 and N3 sleep decreased significantly during ASV therapy, while time spent in N2 sleep significantly increased. The proportion of time in N3 sleep was remarkably low at baseline (4 ± 6% of TST), and decreased further during ASV therapy to 1 ± 4% of TST at follow-up (Table 3). Moreover, 16/30 patients (53%) showed no N3 sleep at baseline and this increased to 26/30 patients (87%) at follow-up. In addition, patients showed a significantly greater proportion of REM sleep at follow-up. Absolute time spent in REM sleep did change significantly from baseline but did show an increasing trend. Fig. 1 shows changes in N3 and REM sleep as a proportion of TST for

Table 1
Baseline characteristics.

Parameter	Patients (n = 30)
Age (years)	71 ± 11
Male (n)	28
BMI (kg/m^2)	28 ± 4
Hypertension (n)	29
Diabetes mellitus (n)	12
Coronary artery disease (n)	21
Implanted rhythm devices (n)	
Pacemaker	2
ICD	10
CRT(D)	5
Echocardiography	
LVEF (%)	33 ± 6
LAD (mm)	51 ± 7
LVEDD (mm)	66 ± 8
Chronic kidney disease (n)	
KDIGO grade 1	5
KDIGO grade 2	10
KDIGO grade3a	8
KDIGO grade 3b	5
KDIGO grade G4	1
Dialysis	1

Numbers are given as means ± standard deviation, or number of patients.
Abbreviations: BMI body mass index; ICD implantable cardioverter defibrillator; CRT(D) cardiac resynchronization therapy (defibrillator); KDIGO Kidney Disease – Improving Global Outcomes; LVEF left ventricular ejection fraction; LAD left atrial diameter; LVEDD left ventricular end-diastolic diameter.

Table 2
Patient characteristics at baseline and follow-up (n = 30).

	Baseline	Follow-up on ASV	*p*-value
NYHA functional class (n)			
II	13	14	n.s.
III	17	16	n.s.
Epworth Sleepiness Scale score	6.3 ± 3.5	5.8 ± 3.7	n.s.
Heart failure medication			
ACE inhibitors (n)	27	27	n.s.
Beta-blockers (n)	28	28	n.s.
Diuretics (n)	24	24	n.s.
Spironolactone/eplerenone (n)	19	17	n.s.
Digitalis glycosides (n)	6	7	n.s.
Antidepressants (n)	4	4	n.s.
Antidiabetics (n)	9	9	n.s.
Blood gas analysis			
pH	7.437 ± 0.032	7.429 ± 0.025	n.s.
pO_2 (mmHg)	80 ± 8	80 ± 8	n.s.
pCO_2 (mmHg)	37 ± 3	37 ± 3	n.s.
NT-proBNP (pg/mL)	5951 ± 18250	4995 ± 15648	n.s.
Creatinine (mg/dL)	1.3 ± 0.5	1.3 ± 0.4	n.s.
Potassium (mmol/L)	4.3 ± 0.5	4.3 ± 0.5	n.s.
Blood pressure (mmHg)			
Systolic	129 ± 30	128 ± 23	n.s.
Diastolic	73 ± 26	74 ± 14	n.s.
Heart rhythm (n)			
Sinus rhythm	18	18	n.s.
Atrial fibrillation	10	10	n.s.
Ventricular pacing	2	2	n.s.
Heart rate at admission (beats/min)	69 ± 12	71 ± 11	n.s.
Mean heart rate during PSG (beats/min)	62 ± 12	60 ± 12	n.s.
SD of heart rate (beats/min)	8 ± 4	8 ± 5	n.s.
SD of RR-interval (ms)	293 ± 150	331 ± 250	n.s.

Numbers are given as means ± standard deviation, or number of patients.
Abbreviations: ACE = angiotensin converting enzyme; ASV = adaptive servo-ventilation; HR = heart rate; n.s. = not statistically significant; NT-proBNP = amino terminal-pro B-type natriuretic peptide; NYHA = New York Heart Association; pCO_2 = carbon dioxide pressure; pO_2 = oxygen pressure; PSG = polysomnography; SD = standard deviation.

Table 3
Respiratory and neurologic parameters.

	Baseline	Follow-up on ASV	*p*-value
Respiratory parameters			
AHI (events/h)	45 ± 16	3 ± 3	< 0.001
ODI (events/h)	33 ± 16	5 ± 4	< 0.001
cAHI (events/h)	35 ± 15	2 ± 3	< 0.001
oAHI (events/h)	7 ± 5	3 ± 3	< 0.001
Central apnoeas (n)	79 ± 80	3 ± 7	< 0.001
Obstructive apnoeas (n)	9 ± 15	0 ± 1	0.002
Mixed apnoeas (n)	8 ± 21	0 ± 0	0.054
Central hypopnoeas (n)	109 ± 81	7 ± 11	< 0.001
Obstructive hypopnoeas (n)	29 ± 25	13 ± 13	0.004
T < 90% (min)	28 ± 45	7 ± 16	0.016
Mean SpO_2 (%)	91 ± 11	91 ± 17	n.s.
Minimal SpO_2 (%)	82 ± 7	85 ± 16	n.s.
Time spent in CSR (%/TST)	22 ± 25	0 ± 0	< 0.001
Neurologic parameters			
TSP (min)	422 ± 56	402 ± 43	n.s.
TST (min)	316 ± 66	313 ± 54	n.s.
WASO (min)	85 ± 52	89 ± 37	n.s.
N1 sleep (min)	102 ± 58	40 ± 14	< 0.001
N1 (%/TST)	34 ± 20	13 ± 5	< 0.001
N2 sleep (min)	141 ± 59	196 ± 44	< 0.001
N2 (%/TST)	44 ± 14	62 ± 7	< 0.001
N3 sleep (min)	13 ± 20	3 ± 12	0.021
N3 (%/TST)	4 ± 6	1 ± 4	0.020
REM sleep (min)	59 ± 34	75 ± 25	0.051
REM (%/TST)	18 ± 8	24 ± 6	0.002
Leg movement arousals (n/h)	1 ± 1	1 ± 3	n.s.
Respiratory arousals/h (n/h)	16 ± 9	1 ± 1	< 0.001
Other arousals/h (n/h)	2 ± 1	3 ± 1	n.s.

Numbers are given as means ± standard deviation.
Abbreviations and definitions: AHI = apnoea-hypopnoea index; cAHI = central apnoea-hypopnoea index; N1, N2, N3 = non-REM sleep stages; n.s. = not statistically significant; oAHI = obstructive apnoea-hypopnoea index; ODI = oxygen desaturation index; REM = rapid eye movement; SpO_2 = oxygen saturation; T < 90% = time spent with an oxygen saturation < 90%; TSP = total sleep period; TST = total sleep time; WASO = wake after sleep onset.

each patient. With consistent suppression of respiratory events during ASV, the number of respiratory-related arousals also decreased, while other arousals remained unchanged.

4. Discussion

This study showed that ASV provided sustained, effective suppression of respiratory events with a reduction in accompanying respiratory arousals. Compared with a healthy population (Ohayon et al., 2004), baseline sleep architecture in our HFrEF patient cohort with CSA-CSR was characterized by a low proportion of restoring N3 but a normal proportion of REM sleep, consistent with similar recent studies (Türoff et al., 2017; Javaheri et al., 2007). Furthermore, we report for the first time that three months of ASV treatment was associated with a significantly increased proportion of REM sleep and a further reduction in N3 sleep. These findings provide new information about potential mechanisms underlying the adverse effects of ASV therapy in patients with HFrEF and predominant CSA.

CSA in HF patients has been shown to be an independent marker for worse prognosis (Oldenburg et al., 2016). Mask-based therapies were developed to treat CSA in HF patients, with ASV being the most efficient. Our finding that ASV effectively ameliorates respiratory events is consistent with previous studies (Oldenburg et al., 2008; Miyata et al., 2012; Szollosi et al., 2006; Oldenburg et al., 2018). However, the SERVE-HF trial found that ASV treatment of CSA was associated with increased all-cause and cardiovascular mortality (Cowie et al., 2015). As a result, ASV therapy is now contraindicated in HF patients with a LVEF < 45% and predominant CSA. However, a recently published large study, The Bad Oeynhausen prospective ASV registry, found that

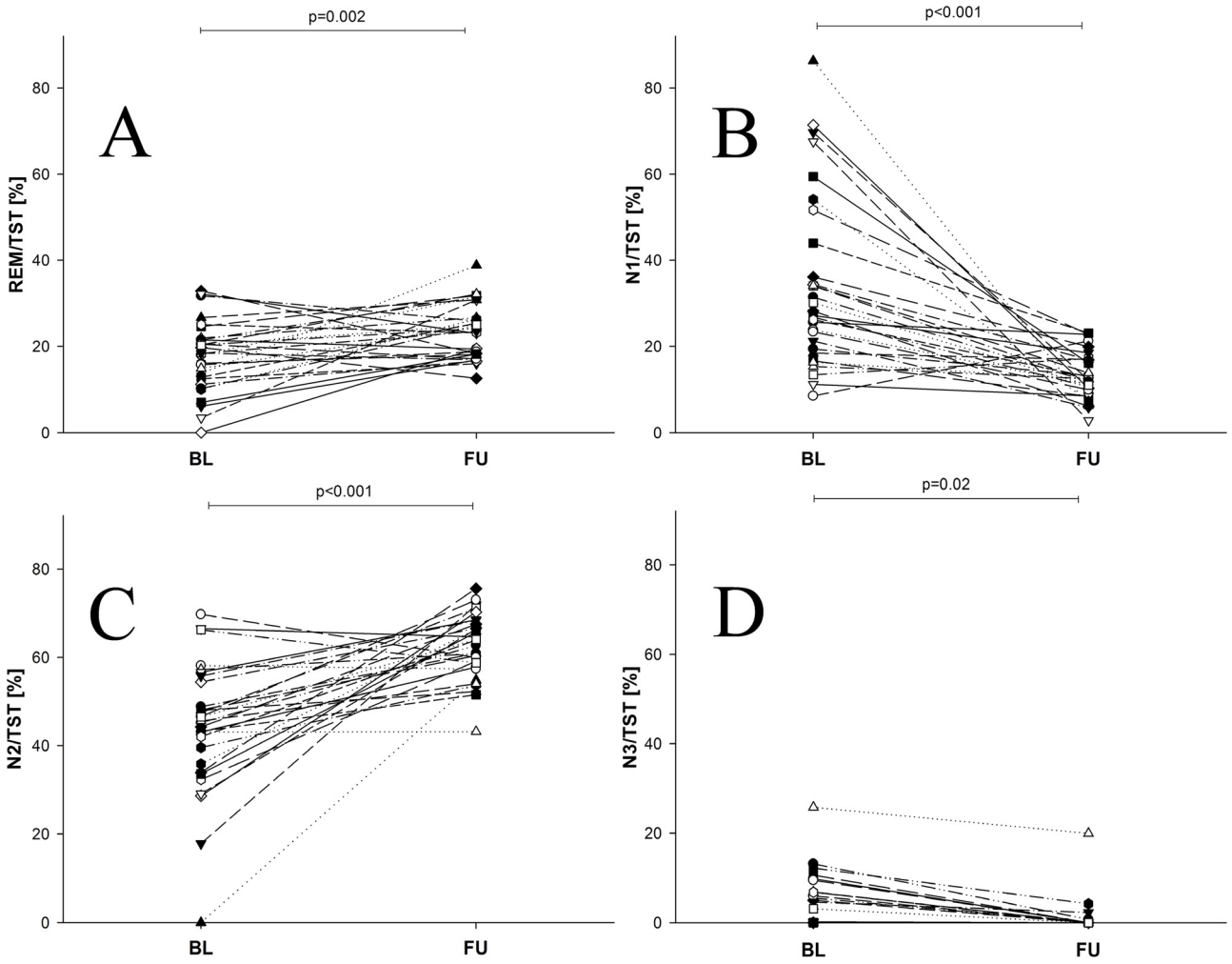

Fig. 1. Proportion of total sleep time (TST) spent in rapid eye movement (REM) sleep (**A**), N1 sleep (**B**), N2 sleep (**C**) and N3 sleep (**D**) for each patient at baseline (BL) and follow-up (FU).

ASV had no impact on survival in HFrEF patients with CSA-CSR (Oldenburg et al., 2018). In addition, data from the registry showed a slight improvement in HF symptoms (NYHA functional class) during use of ASV, without any change in symptoms or objective measures of exercise capacity, LVEF or NT-proBNP levels (Oldenburg et al., 2018).

The findings of the current study with respect to sleep stages contradict those of Teschler et al., who reported large increases in both REM and N3 sleep during ASV therapy (Teschler et al., 2001). However, that study evaluated sleep stages after only one night of ASV usage, providing a possible explanation for the conflicting results. Other studies reporting sleep architecture during short- or long-term therapy showed no significant changes of sleep stages during the use of ASV, but, like our study, also showed a rather low proportion of REM sleep at baseline (< 20%) (Yang and Sawyer, 2016). The significant increase in the proportion of REM sleep seen in our study (to around 24%) could be interpreted as a normalisation of this parameter given that REM sleep proportion in healthy populations is around 20–25% REM, depending on age (Ohayon et al., 2004). In our small study, neither TST nor WASO changed during 3 months' ASV therapy. At baseline, 16 patients in our cohort showed no N3 sleep at all. At 4 ± 6%, the proportion of N3 sleep was markedly reduced compared with the healthy population, who spend about 10% of TST in N3 sleep. Even though ASV effectively treated all respiratory events and reduced respiratory-related arousals in our study, the proportion of N3 sleep at 3-month follow-up was even lower, falling to 1 ± 4% of TST, and 26 patients showed no N3 sleep at follow-up.

In 1993, Somers et al. described interdependencies between SNA, measured directly by microneurography, and different sleep stages (Somers et al., 1993). They reported a significant decline in SNA during N3 sleep, while SNA during REM sleep was similar to that during wakefulness. In N2 sleep, arousal stimuli elicited so called K-complexes, which are frequently associated with bursts of SNA and accompanied by an increase in blood pressure (Somers et al., 1993). Thus, different sleep stages may mirror autonomic nervous activity (ANS) or vice versa. Therefore, changes in sleep architecture might reflect changes in SNA, making it important to investigate the effects of ASV on sleep architecture, especially in patients with HFrEF.

Low proportions of N3 sleep in HFrEF patients, as seen in our study, have been reported previously (Türoff et al., 2017) and might be an indicator of elevated ANS activity, which has been described in these patients (Park and Lee, 2017). At the same time, N2 sleep proportion significantly rises. Furthermore, we observed a higher proportion of REM sleep at follow-up compared with baseline; sympathetic activity is thought to be highest during REM sleep (Somers et al., 1993; Baharav et al., 1995). One possible conclusion is that ASV therapy further increases sympathetic activity during sleep, theoretically increasing SNA.

SNA is currently thought to play a major pathophysiological role in HF. It increases when cardiac function deteriorates, and current guidelines recommend medications that have been shown to reduce SNA activity. It is therefore appropriate that the effects of any HF therapy, including treatments for SDB, on SNA are determined.

Naughton et al. studied sympathetic activity in HF patients with and

without CSA-CSR by measuring urinary and plasma norepinephrine concentrations (UNC and PNC, respectively) (Naughton et al., 1995). They found that patients with CSA-CSR showed significantly less N3 sleep and higher sympathetic activity. After only one month of continuous positive airway pressure (CPAP) therapy with a mean AHI reduction from 48.1 ± 4.9/h to 18.5 ± 6/h, UNC and PNC decreased significantly compared to CSA-CSR patients not treated with CPAP. However, reductions in SNA during CPAP therapy were not associated with significant changes in time spent in different sleep stages (Naughton et al., 1995). While CPAP does not effectively suppress CSA-CSR (Bradley et al., 2005), ASV has been very successful in this respect (Oldenburg et al., 2008; Miyata et al., 2012; Szollosi et al., 2006; Oldenburg et al., 2018).

In contrast to our suggestion of higher SNA during ASV therapy, a reduction in muscule sympathetic nerve activity (MSNA) has been shown in awake patients after in short- and longer- (3.5 months) term ASV usage (Joho et al., 2012; Ushijima et al., 2014). Furthermore, the results of a small randomized controlled study showed a decrease of urinary metanephrine excretion after four weeks of ASV in HF patients (Pepperell et al., 2003), but sleep architecture was not reported in that study. To date, no direct measurements of ANS activity using microneurography during nocturnal ASV therapy have been performed.

Our study has several limitations. In addition to the retrospective design, the study population was small. Furthermore, the HFrEF patients enrolled had various comorbidities in addition to SDB, mostly related to the underlying heart disease, which may influence sleep quality, although patient characteristics did not change between baseline and follow-up.

The goal of this study was to generate a hypothesis and it highlights knowledge gaps in this field. It is essential to identify underlying mechanisms and to understand whether CSA-CSR itself accelerates the progression of HF or whether it is an expression of HF severity. This will facilitate understanding of how CSA-CSR contributes to morbidity in patients with HF. Currently available data are contradictory. Therefore, prospective studies to collect a data on variety of SDB, haemodynamic and nervous system activity endpoints are needed.

5. Conclusion

In conclusion, we found an increase in both REM sleep and light sleep, and less N3 sleep after 3 months of ASV therapy in patients with HFrEF and predominant CSA. These unfavourable changes in sleep stages may explain the absence of quality of life improvements during ASV therapy despite restoration of a normal breathing pattern. Furthermore, these changes might indicate increased sympathetic activity associated with ASV therapy. This could potentially contribute to the adverse events reported in other trials, including the SERVE-HF study.

Author contributions

Concept/design (FR, OO), Data collection (FR, OO) Data analysis/interpretation (FR, OO), Statistics (FR) Drafting article (FR, HF, JS, OO), Critical revision and approval of article (all authors).

Declaration of Competing Interest

R. Tamisier has received lecture fees, research grant and travel grant from ResMed, and travel grants from Agiradom. The other authors declare that they have no conflicts of interest.

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