Clin Res Cardiol (2017) 106:702–710
DOI 10.1007/s00392-017-1112-3

ORIGINAL PAPER

Whom are we treating with adaptive servo-ventilation? A clinical post hoc analysis

Maximilian V. Malfertheiner[1] · C. Lerzer[2] · L. Kolb[1] · K. Heider[1] · F. Zeman[3] · F. Gfüllner[2] · L. S. Maier[1] · M. Pfeifer[1,2] · M. Arzt[1]

Received: 2 February 2017 / Accepted: 7 April 2017 / Published online: 17 April 2017

Abstract
Background Recent evidence has shown that adaptive servo-ventilation (ASV) is contraindicated in patients with predominant central sleep apnea (CSA) and reduced left ventricular ejection fraction (LVEF ≤45%). The objective of this study was to assess the clinical usage of ASV in patients at the time-point of the release of a safety warning by type of SDB, breathing pattern and LVEF.
Methods Patients of a cardiac and a respirology sleep center, both in Germany, who received ASV therapy were contacted between May and October 2015. Retrospective analyses included diagnostic polysomnography, polysomnography with continuous positive airway pressure prior to ASV initiation and echocardiography. Treatment emergent CSA was diagnosed after an appropriate treatment period on CPAP.
Results 285 patients receiving ASV therapy (91 in the cardiac and 194 in the respirology setting) underwent diagnostic polysomnography. 233 (82%) patients had severe SDB, 94 (33%) predominant CSA, and 185 (65%) periodic breathing. 20% ($n = 52$) of patients had an LVEF of ≤45%. The most common indications for ASV were CSA in heart failure (41%) in the cardiac setting and treatment emergent CSA (80%) diagnosed after an appropriate period on CPAP in the respirology setting. The proportion of patients in whom ASV was contraindicated (CSA and LVEF ≤45%) was 16% in the cardiac setting and 9% in the respirology setting.
Conclusion Clinical usage of ASV changed for a small subgroup of patients after release of the SERVE-HF results. Nevertheless, ASV treatment should be monitored and evaluated with diligence in the reminder indications.

Keywords Adaptive servo-ventilation · Sleep-disordered breathing · Heart failure · Cheyne–Stokes respiration · Central sleep apnea

Introduction

Adaptive servo-ventilation (ASV) is a type of non-invasive positive airway pressure (PAP) therapy that differs from the treatment provided by other PAP devices. ASV can be used to treat obstructive and central apnea and hypopnea and to stabilize periodic breathing [1–3]. Therefore, indications for ASV therapy are central sleep apnea (CSA) and simultaneous heart failure, treatment emergent CSA, drug-induced CSA without alveolar hypoventilation, primary CSA, and CSA in stroke patients [4, 5]. The largest group of patients with CSA is patients with heart failure, because 20–30% of patients with chronic heart failure develop CSA [6, 7]. However, according to the study 'Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure' (SERVE-HF) [8], ASV is contraindicated in patients with reduced left ventricular ejection fraction (HFrEF; LVEF

Maximilian V. Malfertheiner and C. Lerzer contributed equally to this work.

✉ Maximilian V. Malfertheiner
maximilian.malfertheiner@ukr.de

[1] Department of Internal Medicine II, Cardiology and Pneumology, Center for Sleep Medicine, University Medical Center Regensburg, Regensburg, Germany

[2] Center for Pneumology, Donaustauf Hospital, Donaustauf, Germany

[3] Center for Clinical Studies, University Medical Center Regensburg, Regensburg, Germany

≤45%) and moderate to severe predominant CSA [9, 10]. SERVE-HF was the first international long-term, randomized, controlled, multicenter phase IV study designed to investigate the effects of adding ASV to guideline-based medical management compared with medical management alone (control). The SERVE-HF study investigated survival and cardiovascular outcome in patients with a LVEF of 45% or less, New York Heart Association (NYHA) class III or IV heart failure or NYHA class II heart failure with at least one heart failure-related hospitalization within 24 months before randomization, and stable, guideline-based medical treatment, who had predominant CSA. Study results yielded significantly higher all-cause mortality and cardiovascular mortality rates in the ASV group than in the control group [8]. A post hoc analysis of the SERVE-HF study showed that—in CSA patients with LVEF ≤30%—ASV therapy markedly increased the risk of cardiovascular death without previous hospital admission [11].

So far, no effective alternative treatment to CSA is available for a considerable proportion of patients at risk on ASV because of predominant CSA and LVEF ≤45% [5, 12]. Unilateral phrenic nerve stimulation that significantly improves CSA, sleep quality and subjective sleepiness [13], may be a promising alternative treatment for a selected group of patients; however, data on cardiovascular outcomes are missing [14]. Therefore, it is of major interest to assess (1) which patient groups do receive ASV therapy and to analyze, (2) the proportion of patients receiving ASV at risk because of predominant CSA and LVEF ≤45% [8] and at high risk because of predominant CSA and LVEF ≤30% [11, 15].

After the release of a safety notice regarding ASV therapy [10], this study was designed to outline the current clinical usage of ASV based on the type of sleep-disordered breathing (SDB), the breathing pattern, and the degree of systolic ventricular dysfunction in a cardiac versus a respirology clinical setting. In addition, we assessed the proportion of patients receiving ASV at risk because of predominant CSA and LVEF ≤45% and at high risk because of predominant CSA and LVEF ≤30%. This would allow it to illustrate the actual impact of SERVE HF on clinical usage of ASV.

Methods

Patients receiving ASV therapy were assessed in the context of a retrospective, bi-centric analysis. Participating centers were the Department of Internal Medicine II at the University Medical Center Regensburg and the Department of Pneumology at the Donaustauf Hospital. The sleep laboratory at the University Medical Center Regensburg is integrated into the Department of Cardiology, whereas the sleep laboratory in Donaustauf has a predominantly respirology background. The analysis included all patients of both centers who had received ASV therapy between 2006 and 2015.

No exclusion criteria applied. All patients were contacted between May and October 2015. Patient records of the first patient visit at the sleep laboratory were assessed that included patient characteristics, medication including opioids and baclofen, comorbidities, diagnostic polysomnography (PSG), CPAP-night by means of PSG monitoring before ASV initiation, and echocardiography results. This retrospective analysis was approved by the Ethics Committee of the University of Regensburg (approval no. 15-101-0255) and conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Polysomnography

Diagnostic PSG and PSG with CPAP before ASV initiation were analyzed. All patients of both centers received PSG using standard techniques as described previously [16]. During PSG, we recorded body position, eye and leg movements, cardiotachography, nasobuccal airflow, chest and abdominal effort, and electroencephalogram (EEG) monitoring. Arterial oxyhemoglobin saturation (SaO_2) was assessed by pulse oximetry. Sleep stages were determined according to the system established by the American Academy of Sleep Medicine (AASM) Manual 2007 and consequent updates [17, 18]. The apnea–hypopnea index (AHI) was defined as the number of apneas or hypopneas per hour of sleep. The oxygen desaturation index was defined as the number of ≥4% oxygen desaturation episodes per hour of sleep. Patients with more than 50% of central apneas from total apneas (cAI/AI) were diagnosed with (predominant) CSA.

Periodic breathing pattern was diagnosed when both of the two following conditions were met: (1) ≥3 consecutive central apnea episodes and/or central hypopnea separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 s (typically lasting 45–90 s), and (2) ≥5 central apnea and/or central hypopnea episodes per hour associated with the crescendo or decrescendo breathing pattern recorded over a minimum of 2 h of monitoring [18]. During the CPAP initiation night, CPAP was initially set to 5 cm H_2O and then titrated upwards in 1 cm H_2O increments until elimination of any sign of flow limitation or reaching maximum patient tolerance. Excessive daytime sleepiness was assessed by the validated German version of the Epworth Sleepiness Scale (ESS) and defined as a score of 11 or higher [19].

Assessment of left ventricular systolic function

An echocardiography is a routine requirement for all patients before polysomnographic diagnostic and treatment of SDB at the participating centers. To diagnose patients with heart failure and reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), a modified definition was applied [8] that stratified heart failure patients with mid-range left ventricular ejection fraction [20] either to the HFrEF group or to the HFpEF group. Patients with symptoms and/or signs of heart failure and LVEF ≤45% were classified as HFrEF. Patients with symptoms and/or signs of heart failure, LVEF >45%, and signs of relevant structural heart disease (left atrial enlargement or diastolic dysfunction) were classified as HFpEF.

Clinical definitions of CSA

Definitions of CSA were applied according to the most recent ERS task force statement on central breathing disturbances during sleep [21] and the International Classification of Sleep Disorders [22].

According to the clinical information available, patients were diagnosed with CSA in heart failure when they had HFrEF or HFpEF and no documented opioid intake [21]. Similarly, CSA in stroke was diagnosed, when a preceding stroke was the best explanation for the occurrence of CSA. The definition for treatment emergent CSA was modified as follows: (a) ≥5/h and predominantly obstructive respiratory events in the diagnostic PSG; (b) significant resolution of obstructive events and emergence or persistence of central events during PAP treatment with a central apnea–hypopnea index of ≥5/h and ≥50% central events; and (c) the phenomenon could not be better explained with another CSA disorder (other than HFrEF or HFpEF) [21]. Drug-induced CSA was determined when CSA occurred in association with drugs that may induce CSA, such as opioids and baclofen. Primary CSA was diagnosed when none of the above causes for CSA applied.

Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD) unless stated otherwise. Baseline patient characteristics of the two groups were compared with two-sided *T* tests for continuous variables and with Chi-square tests for nominal variables. The Fisher's exact test was used if the expected counts were <5. A two-sided *p* value of <0.05 was considered statistically significant. All analyses were done with SPSS Statistic software version 20.0 (IBM, Corp., New York).

Results

In the analyzed period, 285 patients received ASV therapy, 91 in a cardiac setting and 194 in a respirology setting. Patients in the respirology setting had a higher body-mass index (BMI) and significantly more often arterial hypertension (Table 1). Patients of the two centers did not differ with respect to the prevalence of diabetes mellitus or hyperlipidemia. Prescribed medications of HFrEF patients are shown in Table 2.

Diagnostic polysomnography

Diagnostic PSG was evaluated with regard to the severity of SDB by AHI, occurrence of a periodic breathing pattern, and the ratio between central apnea episodes and the total apnea index (cAI/AI). Of the study population of both centers, 82% of patients were diagnosed with severe SDB (AHI ≥30) and 4.5% with mild SDB. The severity of SDB was similar in both settings (Fig. 1a). Predominant CSA (cAI/AHI >50%) was diagnosed in 33% of all patients with a higher proportion in the cardiac than in the respirology setting (63 versus 21%, $p < 0.001$; Fig. 1b). A periodic breathing pattern was identified by means of diagnostic polysomnography in 69% of patients receiving ASV, and the proportion was similar in both settings (72 versus 65%, $p = 0.287$; Fig. 1c).

Polysomnography of the CPAP night before ASV initiation

In the study population, CPAP reduced the AHI by 30%; however, the AHI remained ≥30/h in 56% of patients. The proportion of AHI ≥30/h on CPAP was similar in both settings (Fig. 2a). 67% of patients had predominant CSA (AHI ≥5/h and cAI/AI >50%) during CPAP therapy (Fig. 2a, b). Predominant CSA during CPAP occurred more frequently in patients in the cardiac setting than in patients in the respirology setting (89 versus 56%, $p = <0.001$; Fig. 2b). Regarding patients with HFrEF compared to HFpEF there was no significant difference in occurrence of CSA with CPAP treatment with 27 versus 30%, respectively (Fig. 3). In case of treatment emergent CSA without heart failure a CPAP treatment phase was allowed (median 17 days) to ensure ASV indication due to persisting CSA with CPAP treatment.

Assessment of left ventricular systolic function

Left ventricular function assessed by echocardiography showed that 20% of patients had moderately to severely

Table 1 Patient characteristics at baseline

	Entire population $n = 285$	Cardiac setting $n = 91$	Respirology setting $n = 194$	p value
Age, years	69 ± 9	68 ± 11	68 ± 9	0.616
Male, n (%)	256 (89.8)	86 (93.5)	170 (84.2)	0.083
BMI, kg/m^2	32.2 ± 4.9	30.6 ± 5.8	32.4 ± 4.8	**0.001**
NYHA class				
I or II	210 (74)	36 (67)	174 (89)	**0.001**
III or IV	39 (10)	18 (33)	21 (22)	
Cardiovascular risk factors, n (%)				
Hypertension	239 (90)	60 (65)	179 (92)	**0.011**
Diabetes	97 (35)	34 (37)	63 (32)	0.075
Hyperlipidaemia	162 (57)	54 (59)	108 (55)	**0.015**
Cardiomyopathy	160 (65)	38 (65)	122 (63)	0.95
ICD or CRT	25 (9)	9 (10)	16 (8)	0.307
Pacemaker	32 (11)	11 (12)	21 (11)	0.675

Data are presented as mean ± SD or n (%)

Significant values at $p < 0.05$ are shown in bold

Table 2 Medication of patients with heart failure and reduced ejection fraction (HFrEF) from a cardiac and a respirology setting

HFrEF	Cardiac setting $n = 21$ (%)	Respirology setting $n = 33$ (%)
ACE inhibitor or ARB	18 (86)	29 (88)
Beta-blocker	21 (100)	28 (85)
Loop diuretics	19 (90)	28 (85)
Thiazide	8 (38)	13 (39)
Spironolactone	13 (62)	13 (39)
Digitoxin	4 (19)	7 (21)
Statin	17 (81)	20 (61)
Antiarrhythmics	0 (0)	1 (3)

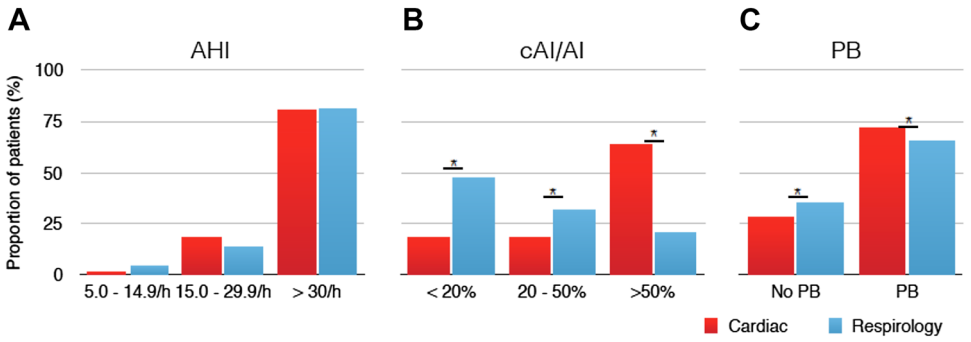

Fig. 1 Diagnostic polysomnography results for severity of sleep apnea indicated by AHI ($n = 285$). Percentage of central apneas from total apneas and proportion of patient with or without CSR. All values are given in percentage. *AHI* apnea–hypopnea index, *cAI* central apnea index, *AI* apnea index, *CSR* Cheyne–Stokes respiration, *PB* periodic breathing pattern. *$p < 0.05$ for the comparison between the cardiac and respirology setting

impaired LVEF (≤45%) and 7% had severely impaired LVEF (≤30%). The proportion of patients with LVEF ≤45% was higher in the cardiac setting than in the respirology setting ($p = 0.046$; Fig. 4a, b). The proportion of patients with severely impaired LVEF (≤30%) was similar in both centers ($p = 0.095$; Fig. 4a, b).

Indications for ASV prescription before the safety notice

In the entire study population, indications for ASV therapy were treatment emergent CSA ($n = 178$, 68%), CSA in heart failure ($n = 59$, 22%), primary CSA ($n = 26$, 10%),

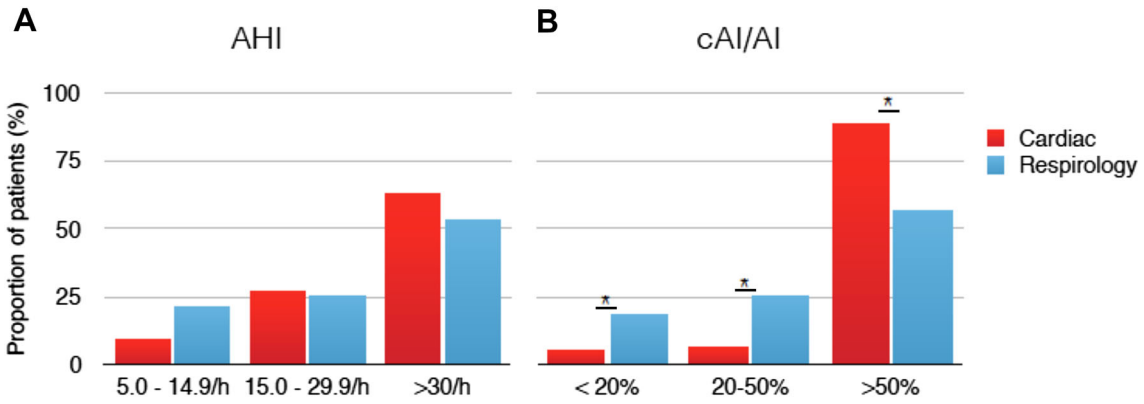

Fig. 2 Polysomnography results with CPAP device showing severity of sleep apnea indicated by AHI ($n = 285$). Percentage of central apneas from total apneas. All values are given in percentage. *AHI* apnea–hypopnea index, *cAI* central apnea index, *AI* apnea index. *$p < 0.05$ for the comparison between the cardiac and respirology setting

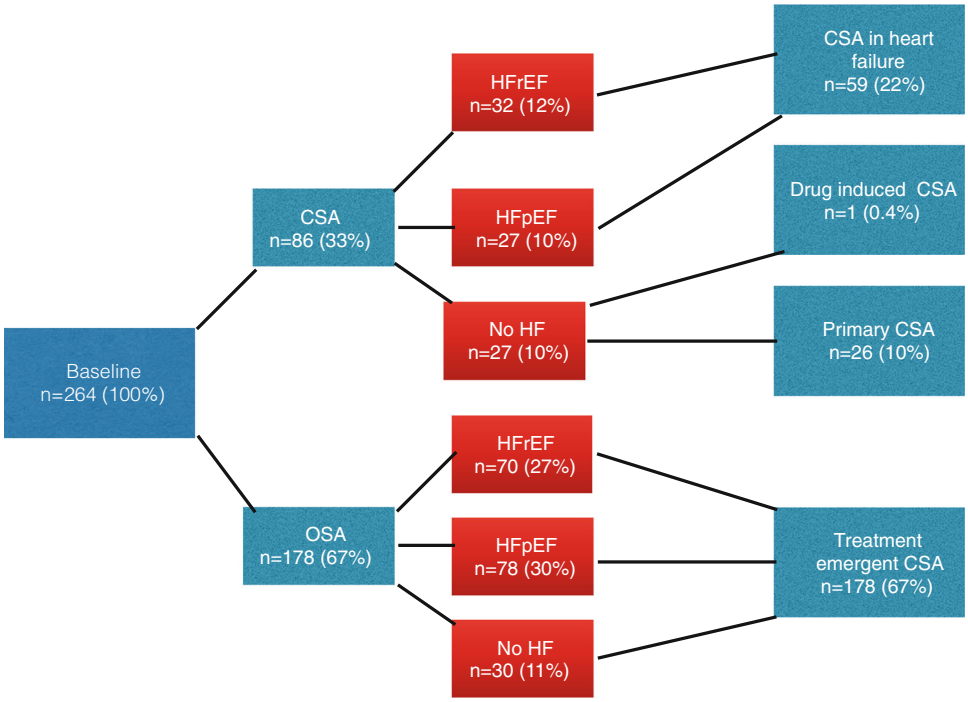

Fig. 3 Flow chart for definition of etiology of central sleep apnea for patients treated with ASV. CSA is defined as cAI >50% of total AI, OSA is defined as cAI ≤50% of total AI according to Randerath et al. [4]. HFrEF is defined by an LVEF ≤45%, HFpEF by LVEF >45% and symptoms of heart failure

and drug (opioid)-induced CSA ($n = 1$, <1%; Fig. 3). CSA in heart failure was a more frequent indication for ASV in the cardiac setting than in the respirology setting (41 versus 15%, $p < 0.001$). However, a higher proportion of patients were diagnosed with predominant OSA at baseline and subsequent treatment emergent CSA in the respirology center than in the cardiac center (80 versus 27%; $p < 0.001$). Interestingly, the majority of patients with treatment emergent CSA had either HFrEF or HFpEF (Fig. 3) in both centers (79 versus 84%, $p = 0.355$; Fig. 3b, c). This finding is in accordance with a recent report from Oldenburg et al. [23]. Patients with LVEF ≤45% and predominant CSA (cAI/AI >50%)—in whom ASV is now contraindicated [8, 9, 21]—represented only 12% of all patients, and the portion was higher in the cardiac than in the respirology setting (16 versus 9%; $p = 0.047$; Fig. 4c, d). Patients receiving ASV who had a markedly increased risk of cardiovascular death (predominant CSA and LVEF <30%) represented 6% of the entire study population. Subsequent to the information that ASV is now contraindicated and withdrawal advised in patients with LVEF ≤45% and predominant CSA [24], only 2 of 32 patients (6%) decided to continue therapy because of the lack of restful sleep without ASV.

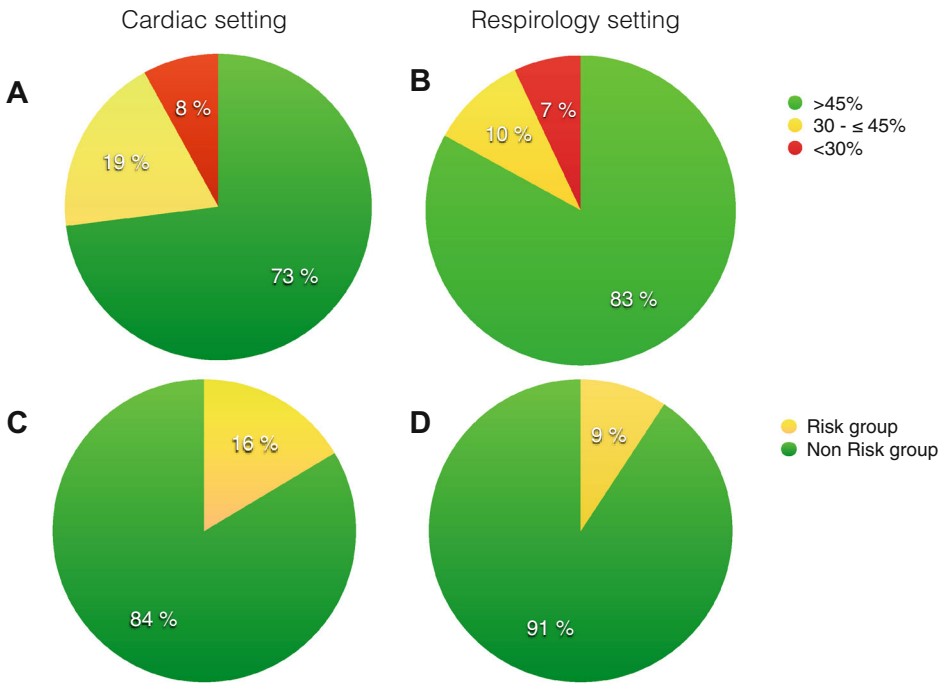

Fig. 4 **a** The distribution of patients according to left ventricular ejection fraction (LVEF) in a cardiac setting. **b** The respirology setting. **c**, **d** The proportion of patients in the risk group for ASV (heart failure with LVEF ≤45% and predominant central sleep apnea) versus patients without contraindication for ASV in the cardiac and respirology setting, respectively

Daytime sleepiness in patients receiving adaptive servo-ventilation

The mean ESS score at baseline was in the normal range both in the cardiac and in the respirology setting (9 ± 5 versus 9 ± 4; $p = 0.922$), indicating the absence of excessive daytime sleepiness (ESS >10) in the majority of patients.

Table 2 shows the proportion of patients diagnosed with excessive daytime sleepiness and moderate or severe sleep apnea (AHI >15, ESS >10) for each phenotype of CSA. 34% of the total study population experienced excessive daytime sleepiness, and this distribution was similar for both treatment emergent and primary CSA. However, more than 50% of patients receiving ASV and diagnosed with CSA in heart failure reported excessive daytime sleepiness (Table 3). No difference in daytime sleepiness could be seen between patients with CSA and HFpEF compared to those with CSA and HFrEF.

Table 3 Percentage of patients with excessive daytime sleepiness according to phenotype of central sleep apnea

	Cardiac setting (%)	Respirology setting (%)
Primary CSA[a]		
ESS >10*	5 (29)	2 (20)
ESS ≤10*	12 (71)	7 (80)
Treatment emergent[a] CSA		
ESS >10[b]	11 (39)	48 (32)
ESS ≤10[b]	17 (61)	102 (68)
CSA in heart failure[a]		
ESS >10[b]	18 (58)	15 (54)
ESS ≤10[b]	13 (42)	13 (46)
All types of CSA[a]		
ESS >10[b]	24 (32)	65 (35)
ESS ≤10[b]	52 (68)	123 (65)

[a] An apnea–hypopnea index (AHI) ≥15/h and >50% central apneas of all apneas indicate an at least moderate degree of central sleep apnea (CSA)

[b] An Epworth Sleepiness Scale score ≥11 indicates excessive daytime sleepiness

Discussion

Novel findings of this retrospective analysis are: (1) the most patients receiving ASV therapy had severe CSA and a periodic breathing pattern at diagnostic PSG, (2) the most common indications for ASV treatment were CSA in heart failure in the cardiac setting and treatment emergent CSA, mostly combined with heart failure, in the respirology setting, (3) less than 20% of patients had an LVEF ≤45%, (4) therefore, the proportion of patients in whom ASV is now contraindicated (predominant CSA and LVEF ≤45%) was low at 16% in the cardiac setting and at 11% in the respirology setting, and (5) less than one third of patients receiving ASV who had at least a moderate degree of CSA experienced excessive daytime sleepiness before treatment initiation.

The vast majority of patients receiving ASV had severe SDB at baseline polysomnography. All patients had persisting or emerging central apnea during CPAP therapy,

hence an indication for ASV therapy, given a CPAP treatment phase in treatment emergent CSA. Previous reports focused on the effect of ASV in different indications such as CSA in heart failure [25], treatment emergent CSA [26], drug-induced CSA without alveolar hypoventilation [27], primary CSA [28], and CSA in stroke patients [29]. This is the first report on a non-selected ASV population from two German centers that gives estimates of the distribution of different indications for ASV in patients receiving ASV in Europe. It has to be noted that these estimates cannot necessarily be generalized for other European countries because of differences in clinical practice and reimbursement systems.

Interestingly, 67% of patients receiving ASV showed predominant OSA in the diagnostic polysomnography. The vast majority (83%) who developed CSA during CPAP therapy had heart failure. These findings are in line with previous studies reporting a proportion of <1% of treatment emergent CSA in patients with OSA in whom heart failure was excluded by measuring brain natriuretic peptide [30] and reported high prevalence of treatment emergent CSA in HFpEF patients [23, 31]. In contrast, in patients with HFrEF and OSA, the prevalence of treatment-emerging CSA was high at 18% [31]. The absence of opioid-induced CSA in a significant number of patients receiving ASV was somewhat surprising, although intake of opioid and baclofen was systematically assessed in both centers. In view of the evidence of the increase in opioid prescriptions in the US and in Europe [32] and the high prevalence of drug-induced opioid users [33], these findings suggest that such patients are not routinely referred for sleep testing and that this entity of CSA has been underdiagnosed in the two study sites. Regarding treatment emergent CSA, it has to be noted that the majority of treatment emergent CSA resolves with ongoing CPAP therapy [34], therefore ASV should be only considered after a period of CPAP treatment of at least 3 months. Patients in our cohort often evolved CSA after a longer time period of CPAP treatment, in mean ASV PSG was performed 370 days (median 11 days) after CPAP PSG.

The results of the SERVE-HF study [8] have caused a paradigm shift in ASV therapy, showing a contraindication for ASV therapy in patients with HFrEF (LVEF ≤45%) and predominant CSA. A recently published post hoc analysis of the SERVE-HF study has shown that in patients with CSA and LVEF ≤30%, ASV therapy is even associated with a more than fivefold increase in the risk of cardiovascular death without previous hospital admission [11]. Beside the SERVE-HF study there is no other RCT on mortality in patients with ASV usage especially there are no safety data on the use of ASV in treatment emergent CSA and HFrEF.

Our data show that 12% of patients receiving ASV were at risk (LVEF ≤45% and predominant CSA) and 6% at high risk (LVEF ≤45% and predominant CSA) because of ASV therapy. The proportion of patients at risk was higher in the cardiac setting than in the respirology setting, which may be explained by referral bias and the participation of the cardiac center in several studies that included HFrEF patients with CSA [2, 8, 12, 33, 35, 36]. Patients at risk are recommended to discontinue ASV treatment. 94% of patients followed this advice and stopped ASV therapy, but two patients continued because of the lack of restful sleep without ASV. Regarding daytime sleepiness, our study population was in accordance with the existing literature, because patients with CSA tend to score lower in the ESS score than patients with OSA [37–40]. Cowie et al. reported a significant lower ESS score in the ASV group but no improvement in quality of life in comparison of the intervention and control group [8]. These findings may have contributed to the fact that the vast majority of risk patients at our cardiac and respirology centers discontinued ASV therapy.

Findings have to be interpreted in the light of the following limitations. This study is a retrospective clinical analysis. Thus, diagnosis of HFpEF was based on echocardiography and clinical symptoms of heart failure (NYHA functional class) in most patients, and NT-proBNP values were not available for all patients [41]. Only routine echocardiography was available in most patients, therefore, often lacking heart cavity dimensions and parameters of diastolic dysfunction. The methodology of scoring sleep studies was significantly different compared to the SERVE-HF study, e.g., only apneas and hypopneas during sleep were considered. It is uncertain, whether our data are representative of patients in other health systems.

Conclusions and clinical implications

Most patients receiving ASV therapy have severe CSA and treatment emergent CSA and a history of heart failure with preserved ejection fraction. ASV therapy is only contraindicated in a minority of patients with HFrEF (LVEF ≤45%) and predominant CSA. In patients with HFpEF or without heart disease, whose normocapnic or hypocapnic CSA cannot be controlled by CPAP, ASV remains an effective therapeutic option [42]. This includes patients with CSA in heart failure (HFpEF), idiopathic CSA, opioid-induced sleep apnea, CSA due to stroke, renal failure or other comorbidities as well as treatment emergent CSA [42]. Therefore, clinical usage of ASV changed for a small subgroup of patients after release of the SERVE-HF results. The recently published results of the cardiovascular outcomes with minute ventilation-targeted adaptive servo-

ventilation therapy in heart failure (CAT-HF) trial suggested a positive effect of ASV in patients with HFpEF in a pre-specified subgroup analysis [43].

Nevertheless, ASV treatment should be monitored and evaluated with diligence in the reminder indications within registries and randomized controlled trials [44].

Acknowledgements We thank Mrs. Monika Schoell for the language editing of this manuscript.

Compliance with ethical standards

Conflict of interest Dr. Arzt reports grants and personal fees from Philips Respironics, grants and personal fees from ResMed, outside the submitted work. All other authors report no conflict of interest.

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