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Adaptive servoventilation in clinical practice: beyond SERVE-HF?

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ABSTRACT Adaptive servoventilation (ASV) has proven effective at suppressing breathing disturbances during sleep, improving quality of life and cardiac surrogate parameters. Since the publication of the SERVE-HF-trial, ASV became restricted. The purpose of this study was to evaluate the clinical relevance of the SERVE-HF inclusion criteria in real life and estimate the portion of patients with these criteria with or without risk factors who are undergoing ASV treatment.

We performed a retrospective study of all patients who were treated with ASV in a university-affiliated sleep laboratory. We reviewed the history of cardiovascular diseases, echocardiographic measurements of left ventricular ejection fraction (LVEF) and polysomnography.

From 1998 to 2015, 293 patients received ASV, of which 255 (87.0%) had cardiovascular diseases and 118 (40.3%) had HF. Among those with HF, the LVEF was ⩽45% in 47 patients (16.0%). Only 12 patients (4.1%) had LVEF <30%. The SERVE-HF inclusion criteria were present in 28 (9.6%) ASV recipients. Of these patients, 3 died within 30–58 months of therapy, all with systolic HF and a LVEF <30%.

In this study, only a small minority of ASV patients fell in the risk group. The number of fatalities did not exceed the expected mortality in optimally treated systolic HF patients.

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The majority of ASV patients do not fulfil the risk criteria. Fatalities under ASV did not exceed expected figures. http://ow.ly/V2HI30fBURh

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Introduction

Sleep disordered breathing (SDB) comprises a variety of pathophysiological and clinical phenotypes [1]. Obstructive sleep apnoea (OSA) is not only characterised by morphological changes of the upper airways, an increase in the critical closing pressure and failing of compensatory muscle function, but also by an increase in the central respiratory drive [2, 3].

Central breathing disturbances can be a consequence of various underlying diseases, mainly cardiovascular disorders, but also renal failure, chronic opioid use, or neurological diseases. Besides the classical subtypes (central sleep apnoea (CSA) and periodic breathing), many patients present with coexisting OSA and central SDB in different combinations. Non-hypercapnic or hypocapnic central breathing disturbances are associated with a shift between hyperventilation and hypoventilation, increased chemosensitivity and brainstem [4–6]. This results in instability of respiration, clinically characterised by a periodic breathing pattern, as in heart failure (HF), high altitude, or treatment-emerging sleep apnoea [1].

Continuous positive airway pressure (CPAP) is the first therapeutic approach for most patients with obstruction of the upper airways and non-hypercapnic CSA [1]. However, it fails in many patients with pure or coexisting central SDB, especially in those with a high loop gain of ventilatory regulation [7]. Adaptive servoventilation (ASV) has been developed to address these complicated situations. It applies positive expiratory pressure to overcome upper airway obstruction, pressure support during inspiration to counterbalance periods of hypoventilation, and mandatory breaths to override central apnoeas [8, 9]. ASV has been used in various entities of central SDB and coexisting obstructive and central sleep apnoea [10–13]. It has proven superior to other treatment options in normalising respiration, improving sleep quality and quality of life, and left ventricular ejection fraction (LVEF) in chronic systolic HF patients [14–16].

Cowie *et al.* [17] studied the effect of ASV on survival in patients with severe systolic HF (HF with reduced ejection fraction: HFrEF) and predominant CSA. Although the study did not show a significant difference between ASV and conventional cardiac therapy in the primary composite cardiac outcome parameter, an exploratory analysis found that ASV was associated with increased death from any cause and death from cardiovascular diseases. Serious concerns were raised regarding the methodology, design and interpretation of the data [18]. Moreover, our experience supports a survival benefit in patients with HFrEF who pursued ASV treatment initiated after hospitalisation for acute cardiac decompensation [19] (Khayat *et al.*, unpublished observations). However, ASV device manufacturers and some health authorities recommend against the use of ASV in patients who fulfil the SERVE-HF inclusion criteria (*i.e.* predominant CSA and chronic systolic HF with substantially reduced LVEF ⩽45%). This recommendation may be difficult to translate in clinical practice for several reasons.

- The predominance of one or another phenotype of SDB is often hard to determine clinically. This particularly applies to hypopnoeas, which are difficult to differentiate accurately (central *versus* obstructive), but represent the majority of the apnoea–hypopnea index (AHI) in most patients. In addition, the precise discrimination of obstructive and central events may require full polysomnography [20].
- Different authors use different percentages of the central AHI/total AHI ratio to define CSA *versus* OSA.
- Baseline echocardiograms for evaluation of the LVEF are not always available.

These practical problems may lead clinicians to unnecessarily withhold ASV from patients without actual risk factors. Therefore, the purpose of this study was to evaluate the clinical relevance of the SERVE-HF inclusion criteria to the practice of sleep medicine in a real-life population and to estimate the portion of patients with or without risk under treatment with ASV.

Material and methods

Patients and design

We reviewed our sleep centre's database to identify all the patients who received ASV between 1998 and 2015. These patients were contacted for participation in the study. Patients then provided demographic, sleep and functional data. In addition, full demographic, objective sleep, cardiovascular and vital data were obtained from medical records. In some cases, outside practitioners or institutions were contacted to obtain required data. We then determined a cohort of ASV recipients who fulfilled the inclusion criteria for SERVE-HF.

A stepwise algorithm was used in identifying the cohort (detailed in figure 1) including the following aspects.

1. Initiation of treatment with ASV
2. Presence or absence of cardiovascular diseases based on patients' history and information from general practitioners or cardiologists
3. Presence or absence of chronic heart failure
4. Presence or absence of LVEF ⩽45%

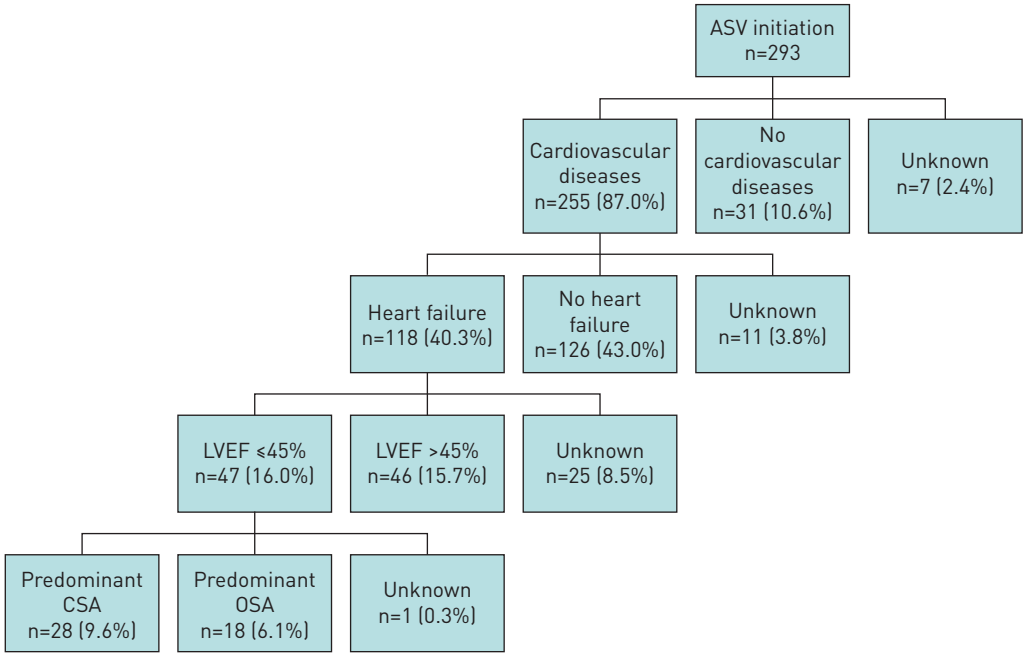

FIGURE 1 Algorithm to define different patient groups. Percentages are of all patients with adaptive servoventilation (ASV) initiation. LVEF: left ventricular ejection fraction; CSA: central sleep apnoea; OSA: obstructive sleep apnoea.

5. Type of SDB and the predominance of central breathing disturbances

Devices

Nine ASV devices from three different manufacturers were used (SomnoVent CR, SomnoVent Auto ST, from Weinmann, Germany; BiPAP autoSV, BiPAP autoSV 2, BiPAP autoSV 2 (with auto-EPAP), BiPAP autoSV Advanced SO, from Philips Respironics, USA; AutoSet CS, AutoSet CS 2, AutoSet CS PaceWave, from ResMed, USA). Every manufacturer provided different generations of development devices with automatic expiratory positive airway pressure (auto-EPAP) and/or a pressure support that can be reduced to zero (Group II) and devices without any of these features (Group I) (table 1).

Polysomnography

All patients underwent in-hospital supervised polysomnography (PSG) for diagnosis and treatment initiation using SOMNOlab (Weinmann, Hamburg, Germany) or Alice 4 or 5 (Philips Respironics, Murrysville, PA, USA) as previously described [11, 20]. An apnoea was defined as the cessation of respiratory flow for ⩾10 s. Central apnoeas were scored if respiratory effort was absent. A hypopnoea was defined as a reduction in nasal pressure signal (flow) of ⩾30% for ⩾10 s accompanied by an arousal and/or a decrease in oxygen saturation of ⩾3%. Hypopnoeas were differentiated based on flattening of airflow, paradoxical breathing, pattern of ventilation, position of arousal relative to SDB and sleep stage, as described previously [20].

Echocardiography

In-house echocardiograms were performed by certified cardiologists (Vivid S 6, GE Healthcare, USA). The LVEF was calculated using Simpson's and/or Teichholz's methods. For all in-house echocardiograms, LVEF was quantified. For a few patients in whom echocardiography was performed externally, we only had a qualitative description of the left ventricular functional status. In this case, we determined the mean value of the functional left ventricular status by using the internationally accepted classification from Lang *et al.* [21]. Here, a normal LVEF is defined as ⩾55%, a slight reduction as 45–54%, a moderate reduction 30–44% and a severe reduction is <30%.

Statistical analysis

Data are given as absolute numbers, proportions or mean (standard deviation), unless stated otherwise. Statistical calculations were carried out with IBM SPSS Statistics (IBM SPSS Statistics for Windows, Version 24.0, IBM, Armonk, NY). Comparisons of more than two groups were done by one-way ANOVA, and Tukey's *post hoc* tests, paired or unpaired t-tests were used to compare two groups, as appropriate.

TABLE 1 Anthropometric data

	Total (n=293)	No risk criteria			Risk group	Risk undefined
		No HF (n=126)	HF EF>45% (n=46)	HF OSA (n=38)	EF⩽45%+CSA (n=28)	EF unknown+CSA (n=5)
Age years	71.9±10.6 (n=293)	71.3±11.1 (n=126)	73.0±6.6*** (n=46)	70.9±9.7$^{\#\#}$ (n=38)	72.6±10.3 (n=28)	74.2±9.3 (n=5)
Minimum $Sa0_2$ %	77.8±10.8 (n=256)	77.4±10.3 (n=102)	80.3±7.4 (n=44)	74.4±12.5$^{\#}$ (n=35)	79.9±12.2 (n=28)	71.8±13.8 (n=5)
AHI h^{-1}	46.0±20.4 (n=259)	48.0±21.2 (n=103)	47.3±22.0 (n=44)	44.2±19.1 (n=37)	44.9±15.2 (n=28)	42.0±16.8 (n=5)
Height cm	173.7±7.9 (n=281)	173.4±8.2 (n=120)	173.2±8.2 (n=44)	173.2±7.5 (n=38)	175.1±8.4 (n=28)	172.7±5.0 (n=3)
Weight kg	96.0±18.0 (n=281)	94.0±17.3 (n=120)	97.2±20.0 (n=44)	100.5±20.2¶ (n=38)	91.2±14.3 (n=28)	113.6±15.1 (n=3)
BMI $kg{\cdot}m^{-2}$	31.8±5.5 (n=281)	31.2±5.1 (n=120)	32.4±5.8 (n=44)	33.4±5.8*,¶¶ (n=38)	29.8±4.5 (n=28)	38.3±7.1* (n=3)
Males/females	264 (90%)/29 (10%)	111 (88%)/15 (12%)	42 (91%)/4 (9%)	35 (92%)/3 (8%)	27 (96%)/1 (4%)	4 (80%)/1(20%)
Group I devices	164 (56%)	77 (61%)	26 (57%)	23 (61%)	10 (36%)	1 (20%)
Weinmann	65 (22%)	33 (26%)	10 (22%)	8 (21%)	4 (14%)	1 (20%)
Respironics	46 (16%)	17 (13%)	10 (22%)	11 (29%)	2 (7%)	0 (0%)
ResMed	53 (18%)	27 (21%)	6 (13%)	4 (11%)	4 (14%)	0 (0%)
Group II devices	117 (40%)	45 (36%)	18 (39%)	15 (39%)	15 (54%)	4 (80%)
Weinmann	3 (1%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Respironics	108 (37%)	41 (33%)	16 (35%)	15 (39%)	15 (54%)	4 (80%)
ResMed	6 (2%)	2 (2%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)

Data are presented as mean±SD unless otherwise indicated. Anthropometric data of the different patient groups according to risk stratification are presented. Group I: devices with autoadjustment of expiratory positive airway pressure (EPAP) and/or a pressure support that can be adjusted to zero (Somnovent CR, BiPAP autoSV, BiPAP autoSV 2, AutoSet CS and AutoSet CS 2); Group II: devices without auto-adjustment of EPAP or a pressure support that can be adjusted to zero (SomnoVent Auto ST, BiPAP autoSV 2 (with auto-EPAP), BiPAP autoSV Advanded SO and AutoSet CS Pacewave). HF: heart failure; EF: ejection fraction; OSA: obstructive sleep apnoea; CSA: central sleep apnoea; $Sa0_2$: arterial oxygen saturation; AHI: apnoea–hypopnoea index; BMI: body mass index. All p-values according to unpaired t-test. *: p<0.05 *versus* no HF; ***: p<0.001 *versus* no HF; $^{\#}$: p<0.05 *versus* HF EF>45%; $^{\#\#}$: p<0.01 *versus* HF EF>45%; ¶: p<0.05 *versus* EF⩽45%+CSA; ¶¶: p<0.01 *versus* EF⩽45%+CSA.

Results

During the study period, ASV treatment was initiated in 293 patients. The mean age was 71.9 years (SD 10.6), the AHI was 46.4/h (20.5/h), the lowest oxygen saturation (SaO_2 min) was 78% (10.8%), and the body mass index 31.8 $kg{\cdot}m^{-2}$ (5.5 $kg{\cdot}m^{-2}$). Out of the patients, 264 (90%) were male and 29 were female (10%) (table 1). The sleep medical diagnoses were CSA (57%), including periodic breathing (36%); OSA (26%); treatment-associated CSA (8%); coexisting obstructive and central sleep apnoea (4%); obesity hypoventilation syndrome (1%); and others (4%).

Of the 293 ASV patients, 255 (87.0%) suffered from at least one cardiovascular comorbidity, including 227 of 255 (89%) with arterial hypertension (table 2), and 118 (46%) of 255 of the patients suffered from systolic or diastolic HF as a consequence of, or in association with, arterial hypertension (87%), coronary artery disease (60%), arrhythmias (47%), aortic valve disease (25%) and dilated cardiomyopathy (15%).

Characteristics of the HF patients in the dataset

LVEF measurements were available in 79% of HF patients (n=118). HFrEF ⩽45% was present in 47 of the HF patients (39.8% of the HF patients; 16.0% of the whole ASV population) (table 3). Predominant CSA

TABLE 2 Cardiovascular diseases in 255 patients with at least one cardiovascular comorbidity

Arterial hypertension	227 (89%)
Heart failure	118 (46%)
Coronary heart disease	103 (40%)
Arrhythmia	84 (33%)
Coronary intervention	64 (25%)
Myocardial infarction	59 (23%)
Aortic valve disease	52 (20%)
Cardiac pacemaker/ICD	36 (14%)
Dilatative cardiomyopathy	18 (7%)

ICD: implantable cardiac defibrillator.

TABLE 3 Left ventricular ejection fraction in the adaptive servoventilation population with heart failure

LVEF ⩽45%	47 (40%)
LVEF >45%	46 (39%)
Not specified	25 (21%)
Normal LV function (LVEF ⩾55%)	33 (28%)
Slightly reduced LV function (LVEF 45–54%)	14 (12%)
Moderately reduced LV function (LVEF 30–44%)	34 (29%)
Significantly reduced LV function (LVEF<30%)	12 (10%)
Not specified	25 (21%)

LVEF: left ventricular ejection fraction; LV: left ventricular.

(more than 50% central AHI) was present in 28 patients with HFrEF ⩽45%, while 18 patients had predominant OSA, and the type of SDB could not be determined in one patient (table 4).

The Epworth sleepiness scale (ESS) decreased from 7.8 (4.5) at baseline to 5.4 (3.7) with treatment ($p<0.001$, pairwise availability of data in 75 cases, time frame 27±26 months) in the HF population. Thirty of 94 patients (32%) had an ESS score ⩾10 pre-treatment, compared to only 15 patients out of 91 (16%) with treatment. Information allowing for assessment of CSA predominance was available in 46 of those cases.

Of all the patients with HFrEF ⩽45%, 28 (9.6%) presented with predominant CSA; 25 of these showed periodic breathing. The LVEF was between 30% and 45% in 20 (6.8% of whole population) patients, while it was <30% in 8 (2.7%). Patients with LVEF ⩽45% and predominant OSA showed a significantly higher index of respiration-related arousals than those with predominant CSA.

All patients who fulfilled the inclusion criteria of HFrEF predominant CSA and those with unclear information were contacted directly or *via* the general practitioner. There were only 3 deaths in the 28 patients who fulfilled the inclusion criteria of SERVE-HF. These 3 patients had LVEF<30%.

TABLE 4 Data from diagnostic polysomnography in patients with left ventricular ejection fraction ⩽45%

	Total (n=47)	Predominant OSA (n=18)	Predominant CSA (n=28)	p-value[#]
TIB min	439.0±40.1 (n=44)	452.6±44.5 (n=16)	431.8±37.6 (n=27)	0.109
SPT min	407.0±57.6 (n=43)	434.7±45.4 (n=15)	392.2±59.8 (n=27)	0.022
TST min	305.3±88.3 (n=43)	333.0±88.4 (n=15)	289.3±87.5 (n=27)	0.130
Sleep efficiency[¶] %	70.5±18.1 (n=43)	74.3±17.7 (n=15)	68.2±18.5 (n=27)	0.307
WASO min	105.9±72.8 (n=43)	101.7±74.5 (n=15)	109.6±74.1 (n=27)	0.742
N1 % TST	28.6±17.8 (n=43)	34.8±21.0 (n=15)	25.7±15.2 (n=27)	0.113
N2 % TST	44.9±16.2 (n=43)	39.9±18.6 (n=15)	47.9±14.6 (n=27)	0.131
N3 % TST	13.6±12.7 (n=43)	10.6±12.7 (n=15)	14.2±11.7 (n=27)	0.363
R % TST	12.9±8.4 (n=43)	14.6±11.1 (n=15)	12.2±6.6 (n=27)	0.378
Minimum $Sa0_2$ in TST %	77.6±14.0 (n=43)	73.1±16.3 (n=15)	80.0±12.4 (n=27)	0.129
Mean $Sa0_2$ in TST %	92.2±3.4 (n=43)	91.9±2.8 (n=15)	92.3±3.7 (n=27)	0.686
$Sa0_2$<90% in TST %	17.4±24.2 (n=44)	20.3±21.6 (n=16)	15.9±26.2 (n=27)	0.469
ODI h^{-1}	40.9±19.4 (n=43)	41.8±21.4 (n=15)	41.0±18.7 (n=27)	0.894
Total AHI h^{-1}	43.1±16.0 (n=47)	41.8±17.0 (n=18)	44.7±15.2 (n=28)	0.551
Central AHI h^{-1}	24.8±16.6 (n=25)	8.8±5.5 (n=9)	33.6±13.5 (n=16)	0.000
Obstructive AHI h^{-1}	15.9±17.1 (n=25)	31.8±18.5 (n=9)	6.9±7.3 (n=16)	0.000
Total AI h^{-1}	23.0±18.0 (n=47)	22.6±20.2 (n=18)	24.0±16.6 (n=28)	0.794
Central AI h^{-1}	12.9±14.2 (n=47)	4.4±4.5 (n=18)	18.8±15.5 (n=28)	0.000
Obstructive AI h^{-1}	6.2±9.5 (n=47)	12.2±12.7 (n=18)	2.5±3.6 (n=28)	0.000
Mixed AI h^{-1}	3.3±8.0 (n=47)	5.7±12.0 (n=18)	1.9±3.3 (n=28)	0.113
Total arousal index h^{-1}	36.7±21.7 (n=40)	43.5±28.1 (n=15)	32.7±16.2 (n=25)	0.129
Respiratory arousal index h^{-1}	22.6±18.7 (n=40)	30.7±25.6 (n=15)	17.8±11.1 (n=25)	0.035

Data are presented as mean±SD unless otherwise stated. OSA: obstructive sleep apnoea; CSA: central sleep apnoea; TIB: time in bed; SPT: sleep period time; TST: total sleep time; WASO: wake after sleep onset; N1: non-REM sleep stage 1; N2: non-REM sleep stage 2; N3: non-REM sleep stage 3; R: REM sleep; $Sa0_2$: arterial oxygen saturation; ODI: oxygen desaturation index; AHI: apnoea–hypopnoea index; AI: apnoea index. [#]: according to t-test, LVEF⩽45% predominant OSA *versus* LVEF⩽45% predominant CSA; [¶]: TST/TIB.

Six patients had stopped treatment, 3 had changed therapy to CPAP, APAP or bilevel. The dates of deaths were available in 2 of 3 patients and happened after 30 and 58 months of ASV therapy.

Discussion

This analysis of a large unselected group of patients treated with ASV showed that only a minority of patients (9.6%) fulfilled the risk criteria as described in the SERVE-HF trial. The majority of patients either did not meet the high-risk criteria or were treated with ASV for indications other than predominant CSA and no change in therapy would have been needed. In this population, ASV was initiated when patients presented with pure CSA or in combination with obstructive disturbances if a treatment with CPAP had failed. Thus, the initiation of ASV was not limited to HF patients.

The SERVE-HF trial investigated the impact of ASV as compared to optimal cardiac care on mortality and serious cardiac events in patients with HFrEF ⩽45% and predominant CSA. Although the study failed to show a difference in the primary combined outcome parameter, the observed excess all-cause mortality and mortality due to cardiovascular events in the ASV group led to safety warnings from healthcare authorities and manufacturers. The SERVE-HF inclusion criteria were generalised as contraindications for the use of ASV. Although these exclusion criteria were precisely defined, clinicians became concerned regarding the use of ASV in general. The purpose of this study was 1) to identify individual patients at risk in order to find clinical solutions for them, and 2) to evaluate the clinical relevance of SERVE-HF in a real-life population.

Although a majority of the patients treated with ASV in our study had at least one cardiovascular disease (87.0%), only 40.3% presented with HF and only 16.0% with HFrEF ⩽45%. More recent analyses of the SERVE-HF data confirmed that the mortality risk is limited to patients with even more severely impaired LVEF. In an adjusted analysis, Eulenburg *et al.* [22] showed that the risk of cardiovascular deaths without previous hospital admission was limited to those with an ejection fraction <30%. Taking these aspects into consideration, the number of patients at risk in our group would be reduced to 2.7%. All three fatalities occurred in the group of patients with LVEF <30%. Available data from these patients showed a treatment period of 30 to 58 months. Based on large, prospective studies, the mortality rate in these patients would be estimated as 25% after 2.5 years, 35–40% after 4 years and 55–60% after 5 years [23, 24]. Thus, there is no indication of an increased number of unexpected deaths. Although this information has to be approached with caution because of the small number of events, it confirms the Eulenburg data limiting the risk – if any – to the patients with most severely reduced LVEF.

The discrimination of obstructive and central disturbances is of crucial importance. Most studies on ASV focus on patients with pure CSA/periodic breathing. However, many patients suffer from coexistence of OSA and CSA with different relative proportions of the phenotypes. In patients with marginal differences between obstructive and central disturbances, in particular, a precise differentiation of the hypopnoeas is of crucial relevance, because they often represent the vast majority of breathing disturbances. For this analysis, we followed the algorithm of hypopnoea differentiation as previously described [20], showing that there was a predominance of CSA in only just over half of the HFrEF patients (28 out of 47).

Our study is limited by its retrospective design. Moreover, information on cardiovascular comorbidities is based on information provided by the patients and general practitioners and our own data files. However, according to the authoritative obligations and the need for optimal patient care, we re-evaluated the patients whenever possible in unclear situations. However, our findings are in line with data from another group [25].

In conclusion, the overwhelming majority of ASV patients are treated for central sleep apnoea and coexisting obstructive and central sleep apnoea without being at risk according to the SERVE-HF trial. Fatalities were limited to the most severe HF patients and did not exceed the estimated numbers.

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