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What is the remaining status of adaptive servo-ventilation? The results of a real-life multicenter study (OTRLASV-study)

Adaptive servo-ventilation in real-life conditions

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Abstract

Backgrounds: As a consequence of the increased mortality observed in the SERVE-HF study, many questions concerning the safety and rational use of ASV in other indications emerged. The aim of this study was to describe the clinical characteristics of ASV-treated patients in real-life conditions.

Methods: The OTRLASV-study is a prospective, 5-centre study including patients who underwent ASV-treatment for at least 1 year. Patients were consecutively included in the study during the annual visit imposed for ASV-reimbursement renewal.

Results: 177/214 patients were analysed (87.57% male) with a median (IQ25–75) age of 71 (65–77) years, an ASV-treatment duration of 2.88 (1.76–4.96) years, an ASV-usage of 6.52 (5.13–7.65) hours/day, and 54.8% were previously treated via continuous positive airway pressure (CPAP). The median Epworth Scale Score decreased from 10 (6–13.5) to 6 (3–9) (p < 0.001) with ASV-therapy, the apnea-hypopnea-index decreased from 50 (38–62)/h to a residual device index of 1.9 (0.7–3.8)/h (p < 0.001). The majority of patients were classified in a Central-Sleep-Apnea group (CSA; 59.3%), whereas the remaining are divided into an Obstructive-Sleep-Apnea group (OSA; 20.3%) and a Treatment-Emergent-Central-Sleep-Apnea group (TECSA; 20.3%). The Left Ventricular Ejection Fraction (LVEF) was > 45% in 92.7% of patients. Associated comorbidities/etiologies were cardiac in nature for 75.7% of patients (neurological for 12.4%, renal for 4.5%, opioid-treatment for 3.4%). 9.6% had idiopathic central-sleep-apnea. 6.2% of the patients were hospitalized the year preceding the study for cardiological reasons. In the 6 months preceding inclusion, night monitoring (i.e. polygraphy or oximetry during ASV usage) was performed in 34.4% of patients, 25.9% of whom required a subsequent setting change. According to multivariable, logistic regression, the variables that were independently associated with poor adherence (ASV-usage ≤ 4 h in duration) were TECSA group versus CSA group (p = 0.010), a higher Epworth score (p = 0.019) and lack of a night monitoring in the last 6 months (p < 0.05).

(Continued on next page)

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(Continued from previous page)

**Conclusions:** In real-life conditions, ASV-treatment is often associated with high cardiac comorbidities and high compliance. Future research should assess how regular night monitoring may optimize devices settings and patient management.

**Trial registration:** The OTRLASV study is registered on ClinicalTrials.gov (Identifier: NCT02429986) on 1 April 2015.

**Keywords:** Adaptive servo-ventilation, Central sleep apnea, Chronic heart failure, CPAP, Obstructive sleep apnea, Treatment emergent central sleep apnea, Sleep-disordered breathing

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**Introduction**

Adaptive Servo-Ventilation (ASV) is a partially automated treatment modality used to correct various types of sleep-disordered breathing (SDB), including periodic breathing [1, 2], but also central and obstructive apnea and hypopnea [3–5]. Current proposed indications for ASV are Treatment-Emergent Central Sleep Apnea (TECSA), Central Sleep Apnea (CSA) associated with stroke, renal failure or other etiologies such as drug induced CSA, co-existing CSA with obstructive sleep apnea (OSA), and idiopathic CSA [5]. For patients with preserved LVEF (left ventricular ejection fraction, i.e. LVEF > 45%) and moderate-to-severe predominant CSA, ASV is an “Option level recommendation” according to the American Academy of Sleep Medicine (AASM) [6], whereas the European Respiratory Society Task Force proposed ASV in this clinical situation (but only after a Continuous Positive Airway Pressure (CPAP) trial failure) [5]. Based on the results of the SERVE-HF study [7], current recommendations underline a consensus against the use of ASV in Chronic Heart Failure (CHF) patients with both reduced LVEF (i.e. LVEF ≤45%) and moderate-to-severe predominant CSA [5, 6].

ASV was initially developed for the treatment of central sleep apnea and Cheyne-Stokes breathing associated with CHF and reduced LVEF [2]. Studies dedicated to these patients are somewhat relatively numerous as compared with other potential indications for ASV [4, 5, 8, 9] and in particular, the only large randomized study in the ASV field concerns these patients (SERVE-HF study, [7]). Paradoxically, the prevalence of related comorbidities/etiologies and sleep apnea patterns for real-life ASV populations has rarely been evaluated [8, 10–13]. Recently, in an unselected monocentric study concerning 293 ASV-treated patients, Randerath et al. reported that only 9.6% of the patients fulfilled the SERVE-HF criteria subtype, thus bringing into question the representativity of the patients included in previously published ASV-studies [13]. As a consequence of the increased mortality observed in the SERVE-HF study, many questions concerning the safety and rational use of ASV in other indications emerged [14].

With the aim of filling the literature gap characterized by a lack of studies describing associated comorbidities/etiolgies for all types of ASV patients, we report here the clinical characteristics of the patients included in the Observational Transversal Real-life Study of ASV (OTRLASV) study. OTRLASV is a multicentric study aimed at describing the clinical characteristics of patients who have undergone ASV for over a year in real-life conditions.

**Methods**

**Study design and study population**

The OTRLASV study is an observational prospective five-expert-centre study (see Additional file 1 for centres) conducted in a exhaustive cohort of consecutive patients treated for at least 1 year with ASV for sleep apnea (SA) (ClinicalTrials.gov Identifier: NCT02429986). The protocol complied with the Declaration of Helsinki and was reviewed and approved by an independent ethics committee (Comité de Protection des Personnes “Sud Méditerranée III”; reference number 2014.11.04).

SA was defined according to the French Social Security rules required for the reimbursement of ASV costs: 1) an Apnoea Hypopnea Index (AHI) ≥ 30/h (or AHI ≥ 15/h and more than 10/h respiratory-effort-related arousal), and 2) associated with sleepiness and at least three symptoms from among snoring, headaches, hypertension, reduced vigilance, libido disorders, nycturia). In order to be reimbursed, the ASV-treated patient needs to be examined each year. Participating investigators enrolled eligible patients (see Additional file 2 for inclusions/exclusion criteria) during this annual visit. Each investigative center was open for 14 months, starting in March 2015. The safety announcement for the SERVE-HF study happened on May 13th, 2015. Prior to this, we included 8 patients (4.5%), and the remaining 169 patients (95.5%) were included after this date, with a last inclusion in January 2017.

**Collected data**

The clinical information collected for the analysis included age, sex, anthropometry, smoking status, blood pressure, initial polysomnography (PSG) or respiratory polygraphy (PG) AHI, Epworth Sleepiness Scale (ESS), number of hospitalizations during the last year (with aetiology), presence of cardiomyopathy (with aetiology and treatment), especially an altered LVEF, cardiological
monitoring, and whether or not the patient knew his/her drug prescription by rote.

The patient status for CHF and LVEF, neurological and renal comorbidities/etiologies, opioid prescriptions were systematically collected. An idiopathic CSA was defined when none of the above causes for CSA applied. ASV treatment modalities were also collected using the manufacturer’s software: usage reported in hours/night for the last 6 months, reported residual AHI by the device (AHItreated), auto-adjusted level of expiratory pressure use versus fixed expiratory pressure, inspiratory and expiratory pressure levels, duration of pressurization, backup frequency, leak level, interface type, use of humidifier, use of heated circuit, and use of a chinstrap. In addition, we collected the treatment initiation time and modality of initiation (hospital or ambulatory conditions), device and interface manufacturer, history of the devices used before ASV, history of the interfaces used. Whether or not night monitoring (a polygraphy / polysomnography / oximetry during ASV for 1 night) had been performed in the last 6 months was also collected, as well as any subsequent changes to device settings and interface choice.

**Initial polygraphy (PG) or polysomnography (PSG) diagnosis and definition of SDB groups**

In line with a recent published real-life study [12], we chose to differentiate central versus obstructive groups using the predominant apnea pattern. Patients with more than 50% of central apneas were classified in the central sleep apnea (CSA) group, while patients with more than 50% of obstructives apneas were classified in the obstructive sleep apnea (OSA) group. Patients with an initial diagnosis of OSA treated with CPAP but secondarily treated with ASV were classified in the Treatment-Emergent Central Sleep Apnea (TECSA) group. Central apnea was scored if respiratory effort was absent. This latter criteria was chosen because it represented a consensus between the different centers and recommendations for scoring (see Additional file 3 for details).

**Echocardiography**

All echocardiograms were performed by senior cardiologists. LVEF was calculated using the Simpson’s and/or Teichholz’s methods. For patients with multiple measures, only the most recent was kept for analysis, and a threshold of a LVEF ≤45% was used to categorize the patient as “reduced” versus “preserved” LVEF, as in the SERVE-HF study [7].

**Statistical analyses**

Data distributions were assessed for normality and continuous data are expressed as means with their standard deviations (SD) or medians and interquartile ranges (IQRs) accordingly. Qualitative parameters were expressed as numbers and percentages. Comparisons between the three SDB-groups (CSA, OSA and TECSA) were performed using ANOVA or Kruskal-Wallis test for quantitative data. Qualitative variables were compared using Chi-square or Fisher test. For significant global comparison, pairwise comparisons were performed using Holm correction for multiple comparison.

The relationship between the date of ASV initiation and delays (since last echocardiography or the last echocardiography) was studied with the Cochran Armitage test. The relationship between the date of ASV initiation and a CPAP trial or a night monitoring in the 6 months preceding the inclusion of the patient in the study was studied using the Jonckheere-Terpstra test. ASV-usage groups were compared by Student’s test or Wilcoxon Mann Withney test for quantitative parameters and Chi-square or Fisher test for qualitative ones. A two-sided p value of < 0.05 was considered as indicating statistical significance.

Multivariable logistic regression analysis was used to study associations between ASV-adherence (≤4 h versus > 4 h) and collected data. Using backward selection, pertinent covariates with a univariable p-value < 0.15 were fed into the multivariable analysis. The α -to-exit was set at 0.05. Odds-ratios with their 95% Wald CI were reported. Model goodness-of-fit was assessed using the Hosmer-Lemeshow test. Missing data have not been replaced. All analyses were conducted by the Department of Research and Medical Information at the Montpellier University Hospitals using statistical software (SAS, V.9.3; SAS Institute; Cary, North Carolina, USA).

**Results**

The flow chart for the study is depicted in Fig. 1. General and sleep characteristics of the population are summarised in Table 1. Briefly, the 177 patients (87.6% male) analysed had a median age of 71 (IQR25–75: 65–77) years, a median body mass index of 29.9 (26.6–34.0) kg/m², and 12% were active smokers (35% had never smoked). The majority of patients was classified in the CSA group (59.3%), whereas the remaining 40.7% were evenly divided into an OSA group (20.3%) and a TECSA group (20.3%) (see Additional file 1 for SDB-group prevalence depending of the enrolment center). SDB-diagnosis was performed by PSG or PG in respectively 42.9 and 57.1% of cases. The median initial AHI for the whole population (WP) was 50/h (38–62), with no difference associated with the diagnosis method (AHITPG of 50/h (39–57) versus AHIPS of 50/h (37–68), p = 0.729).

**ASV**

A CPAP trial was performed before ASV initiation for 37.1% of the CSA group, 57.6% of the OSA group and 100% of the TECSA group (p < 0.001). The delay between
the date of ASV initiation and the existence of a CPAP trial before ASV initiation is depicted in Additional file 4 (p = 0.37). No other mode of ventilation than ASV and CPAP was used.

For the WP, AHI indices significantly improved according to machine-derived values for the ASV treatment group (AHI_{flow} = 1.9/h (0.7–3.8)) versus pre-treatment PG/PSG-derived values (AHI_{PG/PSG} = 50.00 (38.30–62.30)), p < 0.001; Table 1). Significantly decreased final AHI_{flow} values were observed for each SDB group (versus initial AHI_{PG/PSG}, p < 0.001). The median initial Epworth Scale Score (ESS) for the WP was 10 (6–13.5); the final ESS was 6 (3–9). The difference between initial and final ESS was significant for the CSA (p < 0.001) and TECSA groups (p = 0.009), but not for the OSA group (p = 0.068).

ASV initiation was performed at home for 35.3% of the WP, under hospital ambulatory conditions for 19.7 and 45.1% were admitted for continuous hospitalization (no differences were found between SDB groups, p = 0.162).

The median duration of ASV treatment was 2.88 years (1.76–4.96) with no difference between groups. The median ASV-usage for the WP was 6.5 h/day (5.1–7.7). 87.0% of the WP were adherent to ASV for more than 4 h/day. Table 2 depicts the comparison between subgroups of ASV-adherence (≤4 h versus > 4 h) for clinical, ASV or monitoring data. Statistically significant differences existed (1) between SDB groups (p < 0.001), (2) for the presence of PG- or oximetry-based ASV monitoring in the last 6 months (p = 0.014), and (3) for the initial (p = 0.012) and final (p = 0.034) ESS scores.

Multivariable logistic regression analysis was used to study associations between collected data and ASV-adherence (≤4 h versus > 4 h). The following variables (with a p < 0.15 value in the univariate analysis) were included in the multivariable model: SDB-groups, initial ESS, a PG- or oximetry-based ASV monitoring in the last 6 months, a CPAP trial before ASV initiation, an ASV initiation during continuous hospitalization, a neurological comorbidity, and patient treatment knowledge (whether or not the patient knew their treatment). Multivariable logistic regression demonstrated that (1) TECSA group versus CSA group, (2) absence of a PG- or oximetry-based ASV monitoring in the last 6 months and (3) a high initial ESS score were associated with a ≤4 h ASV-adherence (Table 3). In order to rule out a possible confounding effect for the comorbidity/etiology variables, each “comorbidity/etiology” variable was forced into the multivariable analysis but the results were unchanged and “comorbidity/etiology” variables remained statistically non-significant.

**Comorbidities/etiologies reported for ASV-treated patients**

Associated comorbidities/etiologies are depicted in Fig. 2. Comorbidities/etiologies are strictly cardiological in nature for 62% of the patients, only neurological for 4%, and only renal failure for 0.5%. No patient had more than two comorbidities/etiologies and the vast majority
Table 1 General and sleep characteristics of the population

|                  | N | Whole group, n = 177 | CSA group, n = 105 (59.3%) | OSA group, n = 36 (20.3%) | TECSA group n = 36 (20.3%) | P          |
|------------------|---|----------------------|-----------------------------|---------------------------|-----------------------------|------------|
| **Anthropometric data** |   |                      |                             |                           |                             |            |
| Age (years)      | 177 | 71 [65–77]           | 71.00 [65.00–76.00]         | 69.50 [65.00–77.00]       | 74.50 [64.00–83.50]         | 0.447      |
| Gender, n (%)    | 177 |                      |                             |                           |                             | 0.378      |
| Male             | 155 (87.5%) | 93 (88.5%)           | 33 (91.67%)                 | 29 (80.56%)               |                             |            |
| Female           | 22 (12.43%) | 12 (11.43%)          | 3 (8.33%)                   | 7 (19.44%)                |                             |            |
| BMI (kg/m²)      | 175 | 29.90 [26.60–34.00]  | 29.80 [26.55–33.60]         | 29.10 [26.70–35.00]       | 31.55 [26.70–36.05]         | 0.530      |
| **Initial sleep data** |   |                      |                             |                           |                             |            |
| Initial exam     |     |                      |                             |                           |                             |            |
| PG               | 101 | 55 (52.38%)          | 22 (61.11%)                 | 24 (66.67%)               |                             | 0.281      |
| PSG              | 76  | 50 (47.62%)          | 14 (38.89%)                 | 12 (33.33%)               |                             |            |
| Initial AHI (n/h)| 177 | 50.00 [38.30–62.30]  | 50.00 [39.00–67.00]         | 46.80 [34.75–58.50]       | 47.05 [39.00–65.15]         | 0.671      |
| Initial OAII (n/h)| 154 | 7.70 [2.00–18.30]    | 4.00ab [0.90–8.70]          | 16.45b [9.80–21.80]       | 18.45b [7.15–28.15]         | <0.001     |
| Initial CAI (n/h)| 154 | 10.75 [3.60–23.60]   | 17.00bc [9.00–33.80]        | 7.50bc [2.50–9.80]        | 3.50bc [0.65–7.70]          | <0.001     |
| Initial MAI (n/h)| 153 | 1.70 [0.00–5.00]     | 1.50 [0.00–4.65]            | 4.00 [0.00–9.70]          | 0.75 [0.00–7.00]            | 0.279      |
| Initial HI (n/h) | 161 | 16.00 [8.70–24.90]   | 16.75 [8.70–24.30]          | 12.00 [8.35–23.50]        | 17.00 [11.00–27.00]         | 0.641      |
| Initial ESS score| 136 | 10.00 [6.00–13.50]   | 10.00 [6.00–13.00]          | 9.00 [4.00–14.00]         | 12.00 [6.50–13.50]          | 0.598      |
| CPAP trial before ASV initiation, n (%) | 166 | 91 (54.82%) | 36ab (37.11%) | 19bc (57.58%) | 36bc (100%) | <0.001 |

Final sleep data

| Final AHI_{flow} | 177 | 1.90 [0.70–3.80] | 1.80 [0.70–3.30] | 1.95 [0.85–5.35] | 2.25 [0.50–4.80] | 0.448 |
| Final ESS score  | 174 | 6.00 [3.0–9.0]   | 5.00 [3.0–9.0]   | 5.00 [2.0–10.0]   | 6.00 [3.0–10.0]   | 0.731 |

ASV-adherence

Mean adherence > 4 h/day, n (%) | 177 | 154 (87.01%) | 99 (94.29%) | 30 (83.33%) | 25 (69.44%) | <0.001 |

Quantitative variables were described by medians and [IQR_{25–75}]. Significant pairwise comparisons after Holm correction were presented using a for CSA vs. ESA groups, b for CSA vs. OSA groups and c for OSA vs. ESA groups.

AHI Apnea hypopnea index, AHI_{flow} Apnea Hypopnea Index estimated by the device, BMI Body mass index, CAI Central apnea index, CPAP Continuous positive airway pressure, CSA Central sleep apnea, ESS Epworth sleepiness scale, HI Hypopnea index, MAI Mixed apnea index, OAI Obstructive apnea index, OSA Obstructive sleep apnea, PG Poligraphy, PSG Polysomnography, TECSA Treatment emergent central sleep apnea

(24/25) had at least one cardiological comorbidity. No comorbidities/etiologies were reported for 33 patients (18.6%), 51.5% of whom belonged to the CSA group. Thus, 9.6% of the WP can be defined as idiopathic CSA.

Cardiological characteristic

Table 4 depicted the cardiological data of the population. Ischaemic heart failure was present in 34.9% of the WP, 24.6% presented with non-ischaemic heart failure, 30.5% with atrial fibrillation, and 7.3% were diagnosed with a reduced LVEF. For the 147 patients for whom the date of the last cardiological consultation was known, the median delay was 183 days (70–365). Similarly, the median delay since last echocardiography (n = 145) was 263 days (116–529) and appeared to differ between SDB groups (p = 0.015), with a shorter delay for the OSA group (175 days (28–356)). These delays were not dependent on the year of ASV initiation (Additional files 5 and 6, p = 0.19 and p = 0.77, respectively, for consultations and echocardiographic exams). 20.9% of patients were hospitalized the year preceding inclusion, but only 6.2% for cardiological reasons (in detail, six patients were hospitalized for acute (3) or chronic (3) coronary syndrome requiring revascularization by stent (5) or angioplasty (1), 3 patients for acute heart failure, 1 patient for acute atrioventricular block requiring implantation of a pacemaker and 1 patient for a stroke).

Polygraphy and oximetry-based ASV monitoring data

Data for PG- or oximetry-based ASV monitoring performed in the 6 months preceding inclusion are summarised in Table 5. PG on ASV was performed in 31/173 patients, whereas 24/160 patients had overnight oximeter recording on ASV; one patient has both types of control. These controls were associated with a consecutive change in settings for 7 patients in either group (ASV-PG n = 7 and ASV-oximetry n = 7). These changes consisted in a modification of the pressure level for 9 patients, with a modification of the back-up frequency rate for one patient, and a modification of the interface
| Table 2 Comparison between ASV-adherence sub-groups (≤4 h versus > 4 h) for clinical, ASV and monitoring data |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| N                                               | ≤4 h            | > 4 h           | P               |
| Age (years)                                      |                 |                 |                 |
| N = 177                                          |                 |                 |                 |
| Gender                                          |                 |                 |                 |
| n (%)                                           |                 |                 |                 |
| Female                                          |                 |                 |                 |
| 22                                              |                 |                 | 0.316           |
| Male                                            |                 |                 |                 |
| 155                                             |                 |                 |                 |
| Male                                            |                 |                 | 0.316           |
| BMI (kg/m²)                                      |                 |                 |                 |
| N = 175                                          |                 |                 |                 |
| N = 23                                           |                 |                 |                 |
| 29.40 [26.30,32.30]                              |                 |                 | 0.379           |
| SA sub-groups, n (%)                             |                 |                 |                 |
| CSA                                             |                 |                 |                 |
| 105                                             |                 |                 | < 0.001         |
| OSA                                             |                 |                 |                 |
| 36                                              |                 |                 |                 |
| OSA                                             |                 |                 |                 |
| 36                                              |                 |                 |                 |
| TESA                                            |                 |                 |                 |
| 36                                              |                 |                 |                 |
| Initial exam, n (%)                              |                 |                 |                 |
| 177                                             |                 |                 |                 |
| PG                                              |                 |                 | 0.692           |
| PSG                                             |                 |                 |                 |
| 76                                              |                 |                 |                 |
| Initial AH1 (n/h)                                |                 |                 |                 |
| N = 177                                          |                 |                 |                 |
| 50.00 [40.00,67.20]                              |                 |                 | 0.636           |
| Final AH1/low                                    |                 |                 |                 |
| N = 177                                          |                 |                 |                 |
| 2.00 [0.80,5.20]                                 |                 |                 | 0.362           |
| Initial ESS score                                |                 |                 |                 |
| N = 136                                          |                 |                 |                 |
| 12.50 [9.00,16.00]                               |                 |                 | 0.012           |
| Final ESS score                                  |                 |                 |                 |
| N = 136                                          |                 |                 |                 |
| 8.50 [4.00,12.00]                                |                 |                 | 0.034           |
| Initial ESS-final ESS score                      |                 |                 |                 |
| N = 136                                          |                 |                 |                 |
| 2.00 [0.00,6.00]                                 |                 |                 | 0.775           |
| ASV initiation during continuous hospitalization, n (%) |
| N = 173                                          |                 |                 |                 |
| 13                                              |                 |                 | 0.098           |
| CPAP trial before ASV initiation, n (%)          |                 |                 |                 |
| N = 166                                          |                 |                 |                 |
| 16                                              |                 |                 | 0.126           |
| Interface Type, n (%)                            |                 |                 |                 |
| Facial                                           |                 |                 |                 |
| 87                                              |                 |                 | 0.800           |
| Nasal/Nasal Pillows                             |                 |                 |                 |
| 88                                              |                 |                 | 0.759           |
| Cardiological comorbidity/etiology, n (%)       |                 |                 |                 |
| N = 177                                          |                 |                 |                 |
| 18                                              |                 |                 | 0.003           |
| Neurological comorbidity/etiology, n (%)        |                 |                 |                 |
| N = 177                                          |                 |                 |                 |
| 0                                               |                 |                 | 0.053           |
| Renal comorbidity/etiology, n (%)               |                 |                 |                 |
| N = 177                                          |                 |                 |                 |
| 2                                               |                 |                 | 0.036           |
| Opioid comorbidity/etiology, n (%)              |                 |                 |                 |
| N = 177                                          |                 |                 |                 |
| 0                                               |                 |                 | 0.003           |
| Idiopathic CSA, n (%)                            |                 |                 |                 |
| N = 177                                          |                 |                 |                 |
| 2                                               |                 |                 | 1.000           |
| No comorbidity/etiology, n (%)                  |                 |                 |                 |
| N = 177                                          |                 |                 |                 |
| 5                                               |                 |                 | 0.774           |
| Patients with at least one hospitalization for cardiologic cause, n (%) |
| N = 177                                          |                 |                 |                 |
| 3                                               |                 |                 | 0.157           |
| Number of cardiological medications             |                 |                 |                 |
| N = 169                                          |                 |                 |                 |
| 3.00 [1.00,4.00]                                 |                 |                 | 0.535           |
| Knowledge of the medical treatment by the patient, n (%) |
| N = 162                                          |                 |                 |                 |
| 7.00 [4.00,10.00]                                |                 |                 | 0.119           |
| Echocardiography or cardiological consultation in the last 6 months, n (%) |
| N = 144                                          |                 |                 |                 |
| 16.71 [13.61,19.81]                              |                 |                 | 0.294           |
| OxyMetry or Polysgraphy ASV control in the last 6 months |
| N = 157                                          |                 |                 |                 |
| 2                                               |                 |                 | 0.014           |
| Modification of ASV settings as a consequence of Polysgraphy or oximetry, n (%) |
| N = 54                                           |                 |                 |                 |
| 0                                               |                 |                 | 1.000           |

Quantitative variables were described by medians and [IQ18–75] 
AH1 Apnea hypopnea index, AH1/low Apnea Hypopnea Index estimated by the device, BMI Body mass index, CPAP Continuous positive airway pressure, CSA Central sleep apnea, ESS Epworth sleepiness scale, n Number, OSA Obstructive sleep apnea, PG Polysgraphy, PSG Polysomnography, TESA Treatment emergent central sleep apnea, SA Sleep apnea

for 5 patients. The cases where a PG- or oximetry-based ASV monitoring was performed in the last 6 months were not linked with the ASV-initiation date ($p = 0.12$, see Fig. 3).

**Discussion**

In the context of the SERVE-HF study [7], a trial that has raised serious concerns about the effect and safety of ASV, physicians are waiting for new related studies [15].
### Table 3 Logistic regression analysis with adherence (≤ 4 h/day) as the dependent variable. Summary of significant explicative variables

|                                      | Odds ratio [95% CI] | P-value |
|--------------------------------------|---------------------|---------|
| SA groups                            |                     |         |
| TECSA group versus CSA group         | 7.57 [1.063–35.21]  | 0.034   |
| OSA group versus CSA group           | 2.73 [0.49–15.27]   | 0.252   |
| Absence of night monitoring* in the last 6 months | 5.91 [1.003–34.82] | 0.0496  |
| Initial EES score                    | 1.18 [1.03–1.35]    | 0.019   |

*Central sleep apnea, ESS Epworth sleepiness scale, OSA Obstructive sleep apnea, PG Poligraphy, TECSA Treatment emergent central sleep apnea, *night monitoring: polygraphy- or oximetry-based ASV quality monitoring during an ASV night treatment in the last 6 months

Our study provides new data on ASV-use in real-life conditions and new insights for future trials. We report that: 1) the major comorbidity associated with ASV-treated patients after SERVE-HF study remains cardiologic in nature, and concerns 75.7% of patients (but, only 6.2% of the latter were hospitalized for cardiological reasons during the preceding year); 2) 54.8% of the ASV-treated patients previously received a CPAP treatment; 3) 87.0% of the patients were adherent to their ASV for more than 4 h/day; 4) more than a third of the patients included in our study had polygraphy- or oximetry-based monitoring to verify ASV quality in the 6 months preceding inclusion and a consecutive change (device settings or mask type) was performed for 25.9% of them. Interestingly, this monitoring was positively associated with an ASV-adherence > 4 h/jour.

### Conditions associated with ASV

This prospective, real-life study on a non-selected ASV population from five French centers is the first to give data on the related comorbidities/etiologies in “post-SERVE-HF” conditions (see Table 6 to compare with other, similar, real-life studies). In our study, the more prevalent associated comorbidities/etiologies were cardiac in nature for 75.7% of patients (59.5% of the WP present with CHF and 30.5% present with atrial fibrillation). In the Rochester Epidemiology Project (REP) database, a similar high prevalence for cardiac comorbidities/etiologies (78%) and atrial fibrillation (35.9%) was reported, but with less heart failure (34%) [14].

To date, the prevalence of idiopathic CSA is unknown [5]. The 9.6% prevalence of idiopathic CSA found in our study is close to the 10% reported by the recent study from Malfertheiner et al. [12], but differs from the 28% given by the only previous report in 2011 [10]. In the

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Fig. 2 Comorbidities/etiologies associated with ASV prescription. The number and percentages of the total population are presented (1 patient = 0.6%). For 33 patients (18.6%), no comorbidity was related to SA.
### Table 4 Cardiovascular data

|                                      | N    | Whole group, N = 177 | CSA group, N = 105 | OSA group, N = 36 | TECSA group, N = 36 | P     |
|--------------------------------------|------|----------------------|-------------------|-------------------|---------------------|-------|
| Existence of cardiac disease, n (%)  | 177  | 134 (75.71)          | 81 (77.14)        | 26 (72.22)        | 27 (75.00)          | 0.833 |
| Ischaemic HF                         | 175  | 61 (34.86%)          | 37 (35.58%)       | 11 (31.43%)       | 13 (36.11%)         | 0.891 |
| Non Ischaemic HF                     | 175  | 43 (24.57%)          | 26 (25.00%)       | 9 (25.71%)        | 8 (22.22%)          | 0.931 |
| Valvulopathy                         | 175  | 13 (7.43%)           | 4 (3.85%)         | 6 (17.14%)        | 3 (8.33%)           | 0.025 |
| History of AF                        | 174  | 53 (30.46%)          | 32 (31.07%)       | 11 (31.43%)       | 10 (27.78%)         | 0.925 |
| Other cardiac disease                | 175  | 33 (18.86%)          | 18 (17.31%)       | 4 (11.43%)        | 11 (30.56%)         | 0.098 |

### Cardiological monitoring

|                                      | N    | Whole group, N = 151 | CSA group, N = 147 | OSA group, N = 148 | TECSA group, N = 148 | P     |
|--------------------------------------|------|----------------------|-------------------|-------------------|----------------------|-------|
| Cardiological consultation, n (%)   | 151  | 147 (97.35%)         | 89 (95.70%)       | 26 (100.00%)      | 32 (100.00%)         | 0.467 |
| Delay since the last consultation (days) | 147  | 183 [70–365]        | 188.0 [80.0–365]  | 117.5 [24–262]    | 214.5 [125–470]      | 0.070 |
| Cardiological echocardiography, n (%)| 148  | 145 (97.97%)         | 89 (97.80%)       | 25 (100.00%)      | 31 (96.88%)          | 1.000 |
| Delay since the last echocardiography (days) | 145  | 263 [116–529]      | 266 [113–541]     | 175 [28–356]      | 315 [172–665]        | 0.015 |

### Hemodynamic parameters

|                                      | N    | Whole group, N = 149 | CSA group, N = 149 | OSA group, N = 155 | TECSA group, N = 155 | P     |
|--------------------------------------|------|----------------------|-------------------|-------------------|----------------------|-------|
| Systolic BP (mmHg)                   | 149  | 130 [118–140]        | 130.0 [119.0–140.0] | 130.0 [111.0–40.00] | 131.0 [114.0–147.0]  | 0.740 |
| Diastolic BP (mmHg)                  | 149  | 75 [70–82]           | 75.00 [70.00–80.00] | 78.50 [66.00–85.00] | 74.00 [70.00–85.00]  | 0.937 |
| Heart Rhythm (bpm)                   | 155  | 70 [62–77]           | 70.00 [62.00–76.00] | 68.00 [60.00–78.00] | 70.00 [63.00–77.00]  | 0.876 |
| LVEF, n (%)                          | 177  | 13 (7.34%)           | 0 (0.00%)         | 8 (22.22%)        | 5 (13.89%)          | < 0.001 |

### Treatment, n (%)

|                                      | N    | Whole group, N = 164 | CSA group, N = 164 | OSA group, N = 164 | TECSA group, N = 164 | P     |
|--------------------------------------|------|----------------------|-------------------|-------------------|----------------------|-------|
| Diuretic                             | 168  | 73 (43.45%)          | 39 (37.14%)       | 18 (56.25%)       | 16 (51.61%)          | 0.097 |
| Spironolactone                       | 166  | 19 (11.45%)          | 12 (11.65%)       | 4 (12.50%)        | 3 (9.68%)           | 1.000 |
| ACE inhibitor                        | 168  | 61 (36.31%)          | 36 (34.29%)       | 13 (40.63%)       | 12 (38.71%)         | 0.771 |
| β-receptor blocker                   | 168  | 64 (38.10%)          | 38 (36.19%)       | 12 (37.50%)       | 14 (45.16%)         | 0.663 |
| ARB                                  | 165  | 35 (21.21%)          | 24 (23.53%)       | 7 (21.88%)        | 4 (12.90%)          | 0.446 |
| Calcium blocker                      | 169  | 38 (22.49%)          | 23 (21.90%)       | 11 (33.33%)       | 4 (12.90%)          | 0.144 |
| Cardiac glycoside                    | 168  | 2 (1.19%)            | 1 (1.90%)         | 0 (0.00%)         | 0 (0.00%)           | 1.000 |
| Antiarrhythmic drug                  | 168  | 24 (14.29%)          | 12 (11.43%)       | 6 (18.75%)        | 6 (19.35%)          | 0.326 |
| Antiaggregants                       | 168  | 45 (26.79%)          | 25 (23.81%)       | 8 (25.00%)        | 12 (38.71%)         | 0.250 |
| Anticoagulant                        | 168  | 37 (22.02%)          | 22 (20.95%)       | 8 (25.00%)        | 7 (22.58%)          | 0.887 |
| Pacemaker                            | 175  | 22 (12.57%)          | 12 (11.54%)       | 4 (11.43%)        | 6 (16.67%)          | 0.664 |
| ICD                                  | 175  | 7 (4.00%)            | 0 (0.00%)         | 3 (8.57%)         | 4 (11.11%)          | 0.002 |

### Hospitalization during the preceding year

|                                      | N    | Whole group, N = 177 | CSA group, N = 177 | OSA group, N = 177 | TECSA group, N = 177 | P     |
|--------------------------------------|------|----------------------|-------------------|-------------------|----------------------|-------|
| Patients with at least one hospitalization for any cause, n (%) | 177  | 37 (20.90%)          | 19 (18.10%)       | 7 (19.44%)        | 11 (30.56%)          | 0.276 |
| Patients with at least one hospitalization for a cardiologic cause, n (%) | 177  | 11 (6.21%)           | 5 (4.76%)         | 3 (8.33%)         | 3 (8.33%)           | 0.509 |

ACE Angiotensin-converting enzyme, AF Atrial fibrillation, ARB Angiotensin-receptor blocker, BP Blood pressure, CSA Central sleep apnea, HF Heart failure, ICD Implantable cardiac defibrillator, LVEF Left ventricular ejection fraction, OSA Obstructive sleep apnea, TECSA Treatment emergent central sleep apnea

*Quantitative variables were described by medians and [IQ25–75%]. Significant pairwise comparisons after Holm correction were presented using b for CSA vs. ESA groups, c for CSA vs. OSA groups and d for OSA vs. ESA groups.

In particular, the prevalence of idiopathic CSA was only 4.9% [14]. It is impossible to determine if these differences between studies are the consequence of a recruitment bias related to the investigative centers, the absence of collected data or a real change in the prevalence of the comorbidities/etiologies associated with the prescription of ASV. In summary, further studies are needed to confirm the efficacy and safety of ASV in these groups.
Table 5 Data from polygraphy- or oximetry-based ASV quality monitoring performed in the last 6 months preceding the inclusion in the study

|                         | N   | Whole group N = 177 | CSA group N = 105 | OSA group N = 36 | TECSA group N = 36 | P     |
|-------------------------|-----|---------------------|-------------------|------------------|--------------------|-------|
| Polygraphy, n (%)       | 173 | 31 (17.9%)          | 18 (17.5%)        | 7 (20.6%)        | 6 (16.7%)          | 0.897 |
| Apnea Hypopnea Index, (n/h) | 31  | 1.90 [0.4;4.2]      | 1.50 [0.4;2.4]    | 3.5 [0.4;21.9]   | 1.55 [0.2;4.2]     | 0.578 |
| Apnea Index, (n/h)      | 31  | 0.0 [0.0;0.2]       | 0.0 [0.0;0.2]     | 0.10 [0.0;2.70]  | 0.0 [0.0;0.2]      | 0.369 |
| Hypopnea Index, (n/h)   | 31  | 1.9 [0.4;4.3]       | 1.3 [0.4;2.4]     | 3.5 [0.2;11.8]   | 1.5 [0.9;3.9]      | 0.659 |
| ODI 3%, (n/h)           | 30  | 6.9 [3.9;11.6]      | 4.7 [2.4;7.2]     | 9.1 [7.5;23.9]   | 11.3 [4.5;19.9]    | 0.056 |
| Mean SpO2, (%)          | 30  | 95.2 [94.9;96.0]    | 95.5 [94.9;96.0]  | 95.0 [93.0;95.9] | 94.0 [92.7;96.0]   | 0.379 |
| Modification of ASV settings as a consequence of polygraphy, n (%) | 31  | 7 (22.6%)           | 2 (11.1%)         | 3 (42.9%)        | 2 (33.3%)          | 0.138 |
| Oximetry, n (%)         | 160 | 24 (15.0%)          | 17 (17.9%)        | 4 (11.8%)        | 3 (9.7%)           | 0.531 |
| ODI (n/h)               | 24  | 3.2 [1.5;9.7]       | 2.8 [1.9;10.9]    | 3.5 [2.1;5.8]    | 8.7 [1.1;10.7]     | 0.908 |
| Mean SpO2, (%)          | 24  | 93.5 [92.0;94.0]    | 93.1 [91.4;94.0]  | 94.0 [93.0;96.0] | 93.6 [93.0;93.6]   | 0.478 |
| Modification of ASV settings as a consequence of oximetry, n (%) | 24  | 7 (29.2%)           | 6 (35.3%)         | 0 (0%)           | 1 (33.3%)          | 0.519 |

Quantitative variables were described by medians and [IQR25–75%]. CSA Central sleep apnea, ESS Epworth sleepiness scale, ODI Oxygen desaturation index, OSA Obstructive sleep apnea, PG Polygraphy, TECSA Treatment emergent central sleep apnea

ASV prescription, except for a cardiac evaluation to rule out the possibility of a reduced LVEF in CSA patients [5].

CPAP trials as a prerequisite for ASV therapy

For patients with CSA and failure of a recommended first-line CPAP trial, the 2017 European Respiratory Society Task Force systematically proposed ASV therapy as a second line of therapy (except for SERVE-HF pattern patients for whom ASV is contraindicated) [5]. The same recommendation exists for OSA patients [5] (and is a defining characteristic of TECSA patients). In contrast, in 2012, CPAP treatment for CSA patients was only an “Option level” recommendation for the American Academy of Sleep Medicine [7].
| Study Authors | N / C | Main sub-groups analysis reported | Prevalence of related SA comorbidity/etiology | CPAP trial before ASV / ASV-adherence | Duration of ASV / Final AH/1 or AH% /h | Initial AH/h / Final Epworth |
|---------------|------|-----------------------------------|-----------------------------------------------|--------------------------------------|--------------------------------------|---------------------------------|
| Carnevale et al., 2011 [10]. Retrospective | 74 / 2 | 55% non-CHF and 45% CHF | NA CHF with LVEF≤45% and LVEF>45% | 17% N, NA R, NA O, 28% I | 15/74 patients | Duration of the trial NA | 36 ± 18 months | 53.0 ± 23.8/h | 8.9 ± 5.3 |
| Momomura et al., 2015 [11]. Retrospective | 115 / 16 | 24% ASV-discontinued CHF and 76% ASV-continued CHF | NA CHF (LVEF≤45%) and NA CHF (LVEF>45%) | NA N, NA R, NA O, NA I | No CPAP trial | NA | NA | 28.8 ± 19.2/h for ASV-discontinued CHF and 24 ± 21.3/h for ASV-continued CHF/NA |
| Malfertheiner et al., 2017 [12]. Retrospective | 285 / 2 | 32% Cardiac center and 68% Pulmonary center | 39% CHF with LVEF≤45% and LVEF>45% | 0% N, NA R, 0.4% O, 10% ICSA | 1 night for 86 CSA patients and median trial of 17 days for 178 OSA patients | NA | NA | NA |
| Randerath et al., 2017 [13]. Retrospective | 293 / 1 | 57% CSA, 36% OSA, and presence of risk criteria (LVEF ≤45% and CSA) | 16% CHF with LVEF≤45% and LVEF>45% | NA N, NA R, 8% O, NA I | NA | NA | 46.4 ± 20.5/h | 7.8 ± 4.5 |
| Oldenburg et al., 2019 [8]. Retrospective | 224 / 1 | 100% CHF and LVEF ≤45% and AH/h ≥15/h with predominant central pattern | NA | NA | No CPAP trial | 24 months 65.9% > 4 h/day at 24 months | 37.7 ± 13.4 | NA |
| Jaffuel et al. Prospective | 177 / 5 | 59.3% CSA, 20.3% OSA, 20.3% TCSA (11 patients with LVEF≤45% and CSA were excluded) | 7.3% CHF with LVEF≤45% and 51.4% CHF with LVEF>45% | 12.4% N, 4.5% R, 3.4% O, 9.6% I | 91/177 | Duration of the trial NA | 34.5 (21.1–59.5) months | 50/h (38–62) | 10 (6–13.5) |

AH/h Apnea hypopnea index, AH%/h Apnea hypopnea index estimated by the device, CHF Chronic heart failure, CSA Central sleep apnea, TCSA Treatment emergent central sleep apnea, I Idiopathic CSA, LVEF Left ventricular ejection fraction, N/C Number of patients and centres, N Neurological comorbidity/etiology, NA Not available, O Opioid comorbidity/etiology, OSA Obstructive sleep apnea, R Renal comorbidity/etiology, SA Sleep apnea. Results are expressed as means ± SD or medians and quartiles as reported in the original publication.
Here, we report that only 37.1% of the patients in the CSA group and 57.6% of the OSA group had a CPAP trial prior to ASV therapy. The percentage of CPAP trials occurring before ASV initiation remains stable over time, and therefore appears to not be influenced by the different recommendations. In other, similar, published real-life studies (Table 6), the required pre-ASV CPAP trial was not always performed, and when performed, lacked important specifications and/or appropriate duration.

In a recent, large, manufacturer-maintained database, it was surprising to observe that only 3.6% of the 9295 patients treated with ASV were previously treated with CPAP, thus questioning the true prevalence of TECSA-patients treated with ASV [16]. However, this type of manufacturer-database cannot rule out the possibility of a previous CPAP treatment with a different manufacturer, and thus underestimating the TECSA-prevalence. In contrast, the prevalence of TECSA was 75.5% of the ASV-treated patients in the REP database [14]. The exact role CPAP screening among patients eligible for ASV treatment should be detailed in future studies.

**ASV-adherence**

One of the major criticisms of the SERVE-HF study was the weak ASV-adherence of the patients. Indeed, only 47% of the patients were adherent for more than 4 h/day at 1 year (with a mean of only 3.4 h/day). The data presented for the CAT-HF study were even worse, with 2.7 h/day at 6 months [17]). In contrast, 87% of our patients were adherent for more than 4 h/day. This high adherence was also reported by the French study from Carnevale et al. [10], and is likely linked to the reimbursement rules imposed by the French single-payer national insurance system. Unfortunately, ASV-adherence or usage was rarely reported in the other, similar, real-life studies, except for the Oldenburg et al. study (65.9% of patients > 4 h/day at 24 months, see Table 6) [8]. A recent analysis of a large database from the United States confirms a 73.2% ASV-adherence at 3 months for 8957 patients without previous CPAP trials in real-life conditions (ASV-adherence defined by an ASV usage ≥4 h per night, > 70% of nights during the consecutive 30-day period preceding the collection of the data). In the same study, the ASV-adherence at 3 months was 76% for the 209 patients who were previously CPAP treated [16], which is similar to the 69.4% reported in our study.

However, to date, an ASV-usage dependent effect on quality of life has not been demonstrated, as was the case for CPAP [11, 18, 19]. In the CAT-HF trial, the relationship between ASV-adherence (> 3 h) and the burden associated with atrial fibrillation does not reach significance despite a beneficial effect of combined optimal medical treatment (OMT) plus ASV-treatment versus OMT alone [20].

ASV-adherence is of crucial meaning because it is difficult to imagine a potential effect of ASV on strong outcomes (such as quality of life or cardiovascular mobility or mortality) without greater adherence than those reported in the recent ASV-trials [7, 17]. Of course ASV-adherence is a complex parameter, underlined by the on-treatment analysis of the SERVE-HF study. Indeed, Woehrle et al. reported that patients randomised to control who voluntarily switched to ASV had lower cardiovascular mortality than those initially randomised to ASV [21]. In addition, if the increase in cardiovascular mortality is associated with ASV, the risk did not appear to be proportional to the duration of ASV-use [21]. ASV-adherence may not be only a marker of ASV-therapy, but also a marker of a wide-range of patient behaviours toward health and disease. In this regard, it was suggested that ASV usage may be linked to oral medication compliance [22]. For CPAP therapy and OSA patients, two previous studies have reported conflicting results [23, 24]. In our study, we failed to demonstrate a link between the ASV-adherence and the number of cardiological medications or patient knowledge concerning his/her drug treatments. In the REP database, the adherence to ASV at any time was not associated with the rate of change of medication pre-ASV versus post-ASV [14]. Future ASV-randomized studies should assess oral medication compliance in order take to rule out possible bias when interpreting ASV effects [22]. This is one of the major criticisms against the SERVE-HF design study [22].

**Polygraphy and oximetry-based ASV monitoring**

One of the interesting insights from our study concerns the PG- and oximetry-based ASV quality monitoring and the subsequent consequences on settings and ASV-adherence. 34.4% of patients were so monitored, and a consecutive setting change was then performed among 25.9% of them. ASV quality monitoring was not linked to the ASV initiation date, but was favourably associated with ASV-adherence. During ASV therapy, few studies report the correlation and concordance of the AHI measured by PG or PSG and the simultaneous AHI results given by the ASV device (AHIflow) (i.e. real versus device-provided measures). For CPAP, it was underlined that AHIflow was not always correlated or concordant with PG/PSG measures, especially when a 3% versus a 4% threshold of oxygen desaturation is used (results were worse when a PSG was used because of the additive impact of arousals (which cannot be diagnosed by the device) on the scoring) [18, 25–27]. Equivalent, exhaustive data are lacking for ASV therapy, whereas preliminary [28] or final data [8, 29, 30] are in favour of a similar discrepancy between AHIflow and AHIPSG. In the Silveira study, the Bland and Altman plot of the difference between PSG-AHI and ASV-AHIflow against the mean of both measurements, reports a mean difference of 11.9 ± 9.6 (95% limits of agreement – 6.90, 30.71) [30]. In a recent editorial, Thomas and Bianchi have
underlined the existing concern that the efficacy of CPAP and ASV therapies can be overestimated by the reported AHI_{flow} [27]. Future randomized ASV-studies must take into account these considerations by including several PSG controls for ASV quality in the study design. The latter should rule out the consequences of non-optimised ASV therapy on mechanistic parameters such as arousal and desaturation, which are innately underestimated by ASV AHI_{flow}. This is of crucial importance considering the potential ineffectiveness of the device suggested by the literature and the possible consequences on ASV-adherence suggested by our study.

Limits of the study
Our prospective study is a non-randomized observational study with potential unknown sources of bias. Large randomized controlled studies are needed, but a preliminary step is a careful assessment of patients currently treated or potentially eligible for ASV treatment. Observational studies must be multicenter to eliminate bias related to patient recruitment (cf. Additional file 2).

In contrast with recent, similar, real-life studies, our study was not specifically designed to assess the prevalence of SERVE-HF pattern patients in the ASV-treated population. Prevalences of 9 and 12% for SERVE-HF pattern patients were respectively reported in retrospective studies by Randerath et al. [13] and Malfertheiner et al. [12], whereas we report only a 5.8% prevalence. The chronology of our study and the release-date for the SERVE-HF safety notice explains this apparent discrepancy. Our first inclusion occurred in March 2015; the safety notice was released in May 2015. Therefore, our prospective study probably underestimated the prevalence of these patients, because most of the patients stopped their ASV treatment after the safety notice (in this regard, no SERVE-HF pattern patients were included in the 3 centers that joined the study after October 2015). An additional limitation of our study arises from one of the inclusion criteria. Indeed, we were unable to collect the occurrence of spontaneous improvement in central sleep apnea because only patients presenting at the annual control consultation for the continuation of the ASV treatment were included in the study.

Of course, our data may be less relevant to other countries mainly because of governmental policy rules governing ASV-costs. In France, ASV reimbursement at the time of this study was based on a combination of associated clinical symptoms, an AHI-threshold (regardless of apnea and hypopnea patterns) and an ASV-usage > 3 h/day. As a consequence, patients with a diagnostic AHI < 15/h were not treated with ASV, unlike patients included in other real-life studies [11, 12].

The major problem we faced was to classify patients into the CSA and OSA groups according to the results of their PV or PSG exams. As in Malfertheiner et al. [12], we chose to differentiate central versus obstructive SDB groups using the predominant apnea pattern. This choice helped overcome problems caused by changes in scoring recommendations for respiratory events. Indeed, in our study, patient initial diagnoses spanned from 2002 to 2016. During this period, the definition of apnea remained stable, whereas the definition of hypopnea went through major changes, including not only decreased thresholds for the percentage of flow, but also 3% or 4% oxygen desaturation thresholds, and central versus obstructive pattern definitions [31, 32].

In contrast to the consequences of not performing PG- or oximetry-based ASV-night monitoring, we failed to report the consequences of the cardiology consultation and echocardiography (in particular in terms of cardiological therapy or ASV-setting changes). Future trials must record these data because modifications in the cardiological treatment can bias the evaluation of ASV-therapy.

Conclusion
Real-life studies inherently have many biases, but they can help us to better construct randomized studies. Our study reports the updated prevalence of cardiological, neurological, renal and opioid comorbidities/etiologies associated with ASV prescriptions. It emphasizes the need to better define CPAP as a prerequisite for ASV, and emphasizes the need for iterative night-monitoring and cardiological assessments in ASV-treated patients.

Abbreviations
AASM: American Academy of Sleep Medicine; ACE: Angiotensin-converting enzyme; AF: Atrial fibrillation; AHI: Apnea Hypopnea Index; AHI_{flow}: Residual Apnea–Hypopnea-Index measured by the ASV device; APH Marseille: Assistance Publique Hôpitaux de Marseille; APHP Paris: Assistance Publique Hopitaux de Paris; ARB: Angiotensin-receptor blocker; ASV: Adaptive Servo-Ventilation; BMI: Body mass index; BP: Blood pressure; CAI: Central Apnea Index; CHF: Chronic Heart Failure; CHU Dijon: Centre Hospitalier Universitaire de Dijon; CHU Montpellier: Centre Hospitalier Universitaire de Montpellier (CHU Montpellier); CPAP: Continuous Positive Airway Pressure; CSA: Central Sleep Apnea; ESS: Epworth Sleepiness Scale; HII: Hypopnea Index;
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Authors’ contributions
DJ access to the data and takes responsibility for the integrity and accuracy of the analysis. CP and CR have equally contributed to this work. All authors contributed to and approved the final submitted manuscript. DJ: study design, data collection, analysis, and manuscript preparation; CP: data collection, manuscript preparation; CR: data collection, manuscript preparation; JPM: data collection, analysis, manuscript preparation; MG: data collection, manuscript preparation; SR: data collection, manuscript preparation; AP: data collection, manuscript preparation; CMS: data analysis and manuscript preparation; EN: data analysis; NM: study design, data analysis, manuscript preparation; AB: study design, data analysis and manuscript preparation.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The OTRLASV study is registered on ClinicalTrials.gov (Identifier: NCT02429986). The protocol complied with the Declaration of Helsinki and was reviewed and approved by an independent ethics committee (Comité de Protection des Personnes "Sud Méditerranée III", reference number 2014.11.04).

Consent for publication
Not applicable.

Competing interests
Dr. Dany Jaffuel has performed lecturing at sponsored meetings for the following companies in the last 5 years: APARD, Bastide, Loewenstein Medical, Philips, SEFAM. He has sat on advisory boards for the following companies in the last 5 years: Loewenstein Medical, SEFAM. He has received sponsorship support to attend academic meetings in the last 5 years from Loewenstein Medical, Resmed, Philips and SEFAM.

- Dr. Alain Palot has performed lecturing at sponsored meetings for the following companies in the last 5 years: APARD, Philips, Resmed. He has sat on advisory boards for the following company in the last 5 years: Resmed.

- Dr. Claudio Rabec has performed lecturing at sponsored meetings and/or participated in boards for the following companies in the last 5 years: Resmed, Philips, Loewenstein, Air Liquide Medical Systems AB, CMS, CP, EN, JPM, NM, MG, SR report no conflicts of interest in relation to the present work.

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