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SCIENTIFIC INVESTIGATIONS

Effects of Adaptive Servoventilation Therapy for Central Sleep Apnea on Health Care Utilization and Mortality: A Population-Based Study

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Study Objectives: Adaptive servoventilation (ASV) is the suggested treatment for many forms of central sleep apnea (CSA). We aimed to evaluate the impact of treating CSA with ASV on health care utilization.

Methods: In this population-based study using the Rochester Epidemiology Project database, we identified patients over a 9-year period who were diagnosed with CSA (n = 1,237), commenced ASV therapy, and had ≥ 1 month of clinical data before and after ASV initiation. The rates of hospitalizations, emergency department visits (EDV), outpatient visits (OPV) and medications prescribed per year (mean ± standard deviation) in the 2 years pre-ASV and post-ASV initiation were compared.

Results: We found 309 patients (68.0 ± 14.6 years, 80.3% male, apnea-hypopnea index 41.6 ± 26.5 events/h, 78% with cardiovascular comorbidities, 34% with heart failure) who met inclusion criteria; 65% used ASV ≥ 4 h/night on ≥ 70% nights in their first month. The overall 2-year mortality rate was 9.4% and CSA secondary to cardiac cause was a significant risk factor for mortality (hazard ratio 1.81, 95% CI 1.09–3.01, P = .02). Comparing pre-ASV and post-ASV initiation, there was no change in the rate of hospitalization (0.72 ± 1.63 versus 0.79 ± 1.44, P = .46), EDV (1.19 ± 2.18 versus 1.26 ± 2.08, P = .54), OPV (31.59 ± 112.42 versus 13.60 ± 17.36, P = .22), or number of prescribed medications (6.68 ± 2.0 versus 5.31 ± 5.86, P = .06). No differences in these outcomes emerged after accounting for adherence to ASV, CSA subtype and comorbidities via multiple regression analysis (all P > .05).

Conclusions: Our cohort of patients with CSA was quite ill and the use of ASV was not associated with a change in health care utilization.

Keywords: automatic servoventilation, complex sleep apnea, treatment-emergent central sleep apnea, hospitalization, mortality, emergency room, outpatient visits

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Adaptive servoventilation (ASV) is a novel form of positive airway pressure therapy, designed to treat central sleep apnea (CSA). Prior studies demonstrate that treatment of obstructive sleep apnea is associated with decreased health care utilization.

Study Impact: This study is the first assessing the impact of ASV therapy on health care utilization in patients with CSA. In multivariate analysis, no significant change was noted in health care utilization. The comorbidity burden and mortality rate was high, reflecting the ill health of those with CSA in this population-based study.

INTRODUCTION

Adaptive servoventilation (ASV), a positive airway pressure treatment modality capable of providing pneumatic splinting akin to continuous positive airway pressure (CPAP) as well as a variable degree of ventilatory support, was initially designed to treat Cheyne-Stokes breathing (CSB) in heart failure (HF).[1] Prior to this, most efforts to treat CSB involved attempts to utilize CPAP, supplemental oxygen, benzodiazepines and supplemental carbon dioxide and were frequently unsuccessful in resolving these respiratory abnormalites.[2,3] In contrast, ASV provided significantly better control of sleep disordered breathing parameters in patients with CSB compared to oxygen, CPAP, or bilevel positive airway pressure devices. ASV was tested as a treatment modality for other forms of central sleep apnea (CSA), including treatment-emergent central sleep apnea (TECSA) and CSA associated with opioid use.[4–9] These studies clearly demonstrated the superiority of ASV in improving the fundamental metrics of CSA, namely improvement in apnea-hypopnea index (AHI) and stabilization of breathing patterns.

While prior uncontrolled studies with short duration of follow-up demonstrated improvements in ejection fraction (EF), 6-minute walk time, and quality of life with initiation of positive airway pressure therapy in patients with HF and CSA,[10–12] a randomized international multi-center study, the SERVE-HF study, that evaluated the effect of ASV on outcomes in patients with symptomatic systolic HF with CSA, demonstrated increased cardiovascular and all-cause mortality associated with ASV treatment.[13,14] The finding was surprising

and counterintuitive, but led to concerns about outcomes in patients with CSA outside the narrow scope of the SERVE-HF trial inclusion criteria.

A safety alert was issued by the American Academy of Sleep Medicine (AASM) stating that ASV might be contraindicated for patients matching those descriptions (New York Heart Association classes II-IV with an estimated EF ≤ 45% and predominantly CSA). Most sleep centers immediately issued a recall of all patients matching the SERVE-HF study criteria and advised patients to consider discontinuing ASV therapy; however, some investigators noted a decrease in reported quality of life after stopping ASV in patients with HF and CSA/CSB.[15] The AASM evidence-based guidelines continued to recommend ASV as indicated therapy for TECSA and other types of CSA.[2,16] However, the authors concluded that there was very little published evidence regarding the effects on outcomes other than polysomnographic measures. There is a body of evidence demonstrating decreased health care utilization in patients with obstructive sleep apnea (OSA) who are treated but the impact of treatment of CSA on health care utilization is unknown.[17–23]

In this study, we aimed to evaluate the effect of ASV therapy for CSA on health care utilization in a population-based study. We hypothesized that initiation of ASV in patients with CSA would reduce health care utilization, measured by a change in the rate of hospitalizations, emergency department visits (EDV), outpatient visits (OPV) and prescription medication use in the 2 years following commencement of this therapy compared to the 2 years prior to starting ASV. We also examined the association of ASV with mortality, following patients until death or date of last follow-up.

METHODS

Data Abstraction

Population Under Study

We wished to identify all patients residing in Olmsted County who started therapy with ASV for some form of CSA between the January 1, 2007 (the year our center first prescribed ASV) and November 1, 2015. All searches were performed using the Rochester Epidemiology Project (REP) database, a population-based cohort residing in Olmsted County, Minnesota, whose data quality, completeness, reliability and validity have been described previously and which has shown to portray an accurate picture of disease progression and health care utilization in a significantly stable population.[24,25] We did two searches. First, using billing data, we identified those previously diagnosed with any kind of CSA by searching for International Classification of Diseases-9 codes 327.2, 327.20, 327.21, 327.22, 327.24, 327.25, 327.26, 327.27, 327.29. Next, we identified those who underwent diagnostic polysomnography (PSG) using American Medical Association Current Procedural Terminology (CPT) codes 95800, 95801, 95806, 95807, 95808, 95810, 95811, 95782, 95783. These searches identified 1,237 patients who carried a diagnosis of CSA and who had a PSG scored at an AASM-accredited facility that we could use to confirm diagnosis using the definitions below. The medical records, including PSG reports, were reviewed in detail to confirm inclusion criteria were met. To ensure that the records contained information contemporary to patients starting ASV, to be included, patients needed at least one interaction with the health care system 30 days or more prior to starting ASV and at least one interaction 30 days or more following the initiation of ASV. The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards and all participants provided written authorization for use of their medical information for research.

Definitions

A comprehensive review of the chart including clinic notes and investigations was performed by a board-certified sleep medicine specialist (M.P.M.) to ascertain the etiology of CSA and assign subtype in all included patients. For this study, CSA was diagnosed when the central apneas plus central-appearing hypopneas comprised ≥ 50% of the total apneas and hypopneas and the central apnea-hypopnea exceeded 5 per hour on an attended PSG.[26] We defined CSB to be present if this was mentioned in the summary or clinical interpretation of the PSG reports or in the sleep clinic notes by the treating board-certified sleep medicine physician. TECSA was defined as predominantly OSA on the diagnostic study with persistence or development of CSA during positive airway pressure titration. Information regarding obstructive apnea index (OAI), central apnea index (CAI) and minimum oxyhemoglobin saturation was extracted from the diagnostic polysomnogram.

We defined the "index date" as the day ASV was prescribed. ASV adherence at follow-up visits was defined based upon the documentation of downloaded compliance parameters. Full adherence to ASV was defined as ≥ 4 hours use of the device per night on ≥ 70% nights, closest to the time points of 1 month, 3 months and 1 year after the index date. Those using ASV but not achieving ≥ 4 hours use nightly on ≥ 70% of nights for at least 1 month were categorized as partially adherent and those reporting no use at all as nonadherent. Adherence was marked as unknown if there was no follow-up at the sleep center and/or no device download information available.

Demographic and Comorbid Conditions

We recorded the age, body mass index (BMI), and past or current history of smoking, and comorbidities at the ASV index date. We also recorded diagnoses of comorbidities any time after the index date. Electrocardiograms, Holter monitor reports, echocardiograms, and intensive care notes were all reviewed for any mentions of paroxysmal atrial fibrillation. If there were multiple echocardiograms performed on a single patient, the recorded EF was taken from the transthoracic or transesophageal echocardiogram conducted closest to the PSG diagnosing CSA. The cause of death was noted from the death certificates.

Determination of Health Care Utilization

All outpatient clinic, ER and hospital notes were reviewed for the 2-year period prior to and after the index date. We counted the number of visits, date/site of visit, classified the type of hospital admission (unplanned versus elective) and cause of the

first five hospitalizations for each patient before and after the index date. For EDV and OPV, if there were more than one visit on the same day, each was counted as a separate visit. All face-to-face visits with a health care provider, eg, for blood pressure checks, intra-articular steroid injections, cast/splint application were counted, but not appointments for laboratory tests including international normalized ratio checks. The number of OPV before and after ASV was extracted on a random sample of 52 patients in the cohort. The number of prescription medications was tabulated at the date most proximal to the index date. Oral, per rectal, transdermal, injected and inhaled medications were included. In this study design examining health care utilization 2 years prior and 2 years after the use of ASV, there may have been some time when the patient did not reside in Olmsted County. The REP allowed identification of such periods of time so that they could be removed from the analyses. Any patient who died during the 2-year period following ASV was considered to be under observation and at risk of hospitalization up until the date of death.

Outcomes

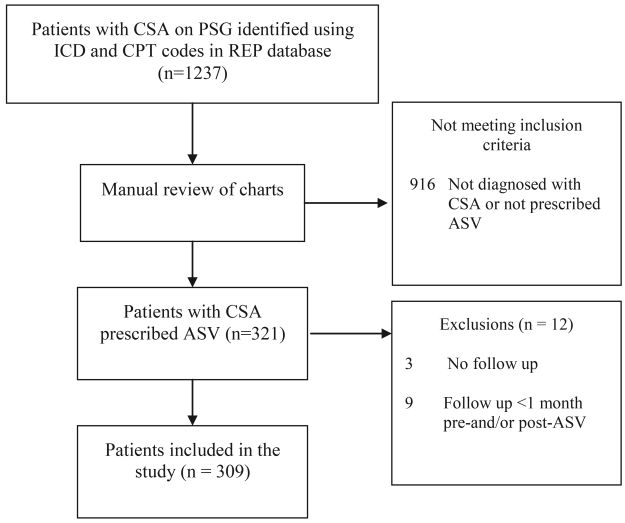
The change in hospitalization rate before and after starting ASV was considered the primary outcome, and the change in the number of EDV, OPV and number of prescription medications were secondary outcomes. The hospitalization rate was calculated as the number of all hospitalizations observed divided by the interval of time (up to a maximum of two years) that the individual was believed to reside in the county. The rate for hospitalizations, EDV and OPV was estimated for each patient by calculating the number of events identified during the observation period divided by the duration of time observed.

Statistical Analyses

The univariate analyses of the change in hospitalization rates between pre-ASV and post-ASV periods of observation were performed and reported using a paired *t* test (results using the Wilcoxon signed-rank test were found to be consistent). Rates were expressed as mean ± standard deviation (SD). A linear regression model was used in a multiple variable model including CSA category as well as baseline covariates. In this model, the change in hospitalization rate from pre-ASV to post-ASV was the dependent variable. With 200 patients, there was 80% power to detect an effect size of ≥ 0.20 in the pre-ASV and post-ASV period hospitalization rate assuming a paired *t* test.

Overall survival following ASV therapy was estimated using the Kaplan-Meier method with univariate and multiple variable associations assessed using a Cox proportion hazards model. Patient survival status was identified using Accurint (http://www.accurint.com/; LexisNexis, New York City, New York, United States). Patients not having a death date retrieved were assumed to be alive as of October 1, 2017. Patient factors such as age, sex, BMI, AHI and other comorbidities (smoking status, systemic hypertension, coronary artery disease [CAD], HF, stroke, AF, diabetes mellitus, chronic obstructive pulmonary disease [COPD], antidepressant use and mild cognitive impairment/dementia) were included in multiple variable models to account for possible confounders. Further analyses were performed in patients categorized by CSA subtype and by objective adherence to treatment which was determined based on ASV device download. For the outcome of death, with 91 deaths there was 80% power to detect a hazard ratio of ≥ 1.8. All analyses were done using SAS version 9.4M3 (SAS Institute Inc., Cary, North Carolina, United States). The two-tailed alpha-level was set at .05 for statistical significance. These analyses were repeated after removing participants with a known EF of ≤ 45%.

Figure 1—Flowchart showing patients included in the study.



ASV = adaptive servoventilation, CPT = Current Procedural Terminology, CSA = central sleep apnea, ICD = International Classification of Diseases, PSG = polysomnography, REP = Rochester Epidemiology Project.

RESULTS

A total of 309 patients were included (**Figure 1**). Most exclusions were patients erroneously coded as CSA (who upon review of the medical record had a diagnosis of OSA or other conditions) and those with CSA that were not prescribed ASV as initial therapy for use at home after PSG. Nine patients did not have the minimum requisite period of clinical data in the electronic medical record for 1 month pre-ASV and/or post-ASV and 3 patients had no follow-up notes in the medical record after the PSG. All included patients were diagnosed with CSA and prescribed ASV at our tertiary health care center, typically the first working day following PSG. The median time to prescription of the ASV device from the time of diagnosis of CSA was 8 days (interquartile range 1 to 33 days).

Baseline patient characteristics, comorbidities, CSA subtypes and adherence to ASV therapy are outlined in **Table 1**, **Table 2**, and **Table 3**. TECSA was the most common subtype, seen in 73% of the cohort. Participants with CSA related to cardiac disease were categorized into those in whom CSB was noted and those in whom no CSB pattern was noted on PSG. Participants with miscellaneous causes of CSA such as central

Table 1—Patient characteristics at the time of ASV initiation (n = 309).

Characteristic	
Age (years), mean (SD)	68.0 (14.6)
Sex (male), %	80.3
Ethnicity (white), %	97.1
Smoker (past/current), %	55.7
Apnea-hypopnea index (events/h), mean (SD)	41.6 (26.5)
Central apnea index (events/h), mean (SD)	13.9 (20.2)
Body mass index (kg/m^2), mean (SD)	31.7 (6.5)
Systemic hypertension, %	78.0
Coronary artery disease, %	48.9
Heart failure, %	34.0
Stroke, %	14.2
Atrial fibrillation, %	35.9
Diabetes mellitus, %	31.4
Chronic obstructive pulmonary disease, %	14.6
Antidepressant use, %	31.7
Mild cognitive impairment/dementia, %	11.7

ASV = adaptive servoventilation, SD = standard deviation.

Table 2—CSA subtype (n = 309).

CSA Subtype	n (%)
Treatment-emergent CSA	224 (75.5)
CSA with CSB	34 (11.0)
CSA secondary to cardiac cause (no CSB)	20 (6.5)
Opioid-induced CSA	4 (1.3)
Primary CSA	15 (4.9)
Multiple/other etiologies	12 (3.9)

CSA = central sleep apnea, CSB = Cheyne-Stokes breathing.

Table 3—Adherence to ASV.

Adherence at 1 month (n = 309)	n (%)
Partial, no/unknown	109 (35.3)
Full (≥ 4 hours nightly on ≥ 70% nights)	200 (64.7)
Adherence at 3 months (n = 307)	
Partial, no/unknown	168 (54.7)
Full (≥ 4 hours nightly on ≥ 70% nights)	139 (45.3)
Adherence at 1 year (n = 298)	
Partial, no/unknown	211 (70.8)
Full (≥ 4 hours nightly on ≥ 70% nights)	87 (29.2)
Adherence at all 3 time points (n = 298)	
Partial, no/unknown	241 (80.9)
Full (≥ 4 hours nightly on ≥ 70% nights)	57 (19.1)

n values reflect the number of patients still alive at each follow-up time point. Adherence at all three time points uses the data from the 298 patients still alive at the 1-year time point. ASV = adaptive servoventilation.

nervous system disorders or those with more than one potential etiology for CSA were designated as having "multiple/other" causes for CSA. For the purposes of statistical analyses, patients were grouped into "TECSA," "cardiac-related CSA" and "other" due to the relatively small number of patients in the non-treatment emergent and non-cardiac related CSA subtypes. A total of 139 (45%) patients utilized their ASV device for ≥ 4 hours on ≥ 70% nights in the preceding ≥ 30 days at approximately 3 months and 88 (28.5%) at approximately 1 year following the commencement of ASV.

Seventy (22.7%) of the 309 patients had a complete 2-year period of data in the electronic medical record pre-ASV and a total of 280 (90.6%) of 309 patients had complete follow-up data available for 2 years following ASV. Those who died before 1-month, 3-month and 1-year follow-ups were excluded from the analyses evaluating adherence to ASV at these three time points respectively.

Hospitalizations Pre-ASV and Post-ASV Initiation

A total of 137 of 309 patients had ≥ 1 hospitalization pre-ASV and 151 patients had ≥ 1 hospitalization post-ASV. One hundred three patients had no hospitalizations either pre-ASV or post-ASV. A total of 291 hospitalizations were identified during 534.0 person-years of observation pre-ASV, while a total of 418 hospitalizations were identified during 594.1 person-years of follow-up post-ASV. The hospitalization rate pre-ASV was 0.72 ± 1.63 per year and post-ASV was 0.79 ± 1.44 per year (P = .46).

On univariate analysis, increasing BMI (P = .009) and HF (P = .002) were both associated with a change in hospitalization rate pre-ASV to post-ASV, while age, sex, AHI, OAI, CAI, minimum oxyhemoglobin saturation, smoking status, CSA subtype, other comorbidities including hypertension, CAD, AF, DM, stroke, COPD, antidepressant use and adherence to ASV at time points closest to 1 month, 3 months and 1 year following commencement of the device were not (all P > .05).

There was no significant difference in the rate of hospitalization prior to and following commencement of ASV after adjusting for CSA subtype, full adherence to ASV at 1 month and following multivariate analyses accounting for age, sex, BMI, HF, AF, COPD, CSA subtype and full adherence to ASV at 1 month (**Table 4**).

There was no difference in the proportion of elective versus unplanned hospitalizations when comparing the first five hospitalizations in the 2 years before and after commencement of ASV. Similarly, there appeared to be no difference in unplanned cardiovascular or respiratory-related hospitalizations versus all other hospitalizations prior to and after commencement of ASV.

Emergency Department Visits Pre-ASV and Post-ASV Initiation

A total of 190 of 309 patients had at least one EDV pre-ASV and 183 had at least 1 EDV post-ASV, with 62 patients having no EDV either pre-ASV or post-ASV. A total of 584 EDV were identified during 534.0 person-years of observation pre-ASV and 702 EDV in 594.1 person-years of follow-up post-ASV. The EDV rate pre-ASV was 1.19 ± 2.18 per year and post-ASV was 1.26 ± 2.08 per year (P = .54).

In univariate analyses, age (P = .01), BMI (P = .01), CAD (P = .03) and HF (P = .07), but not CSA subtype (P = .09), were associated with the change in the rate of EDV per year pre-ASV to post-ASV. Sex, AHI, CAI, OAI, minimum

Table 4—Multivariate analyses for rates of hospitalization, emergency department visits, outpatient visits and medications pre-ASV versus post-ASV.

Variable	Parameter Estimate*	Standard Error	*P*
Hospitalization rate pre-ASV versus post-ASV			
Age, per 1 year	−0.00264	0.00856	.76
Male sex	0.03476	0.25597	.89
Body mass index, per 1 point	0.03840	0.01708	.03†
Cardiac comorbidity [a]	−0.42761	0.22537	.06
Chronic obstructive lung disease	−0.17845	0.28447	.53
CSA secondary to cardiac cause ± CSB [b]	0.24502	0.28990	.40
CSA secondary to opioids/multiple/other causes [b]	0.33446	0.34363	.33
Full adherence to ASV at 1 month	0.10322	0.21240	.63
Emergency department visit rate pre-ASV versus post-ASV			
Age, per 1 year	−0.01298	0.01045	.22
Male sex	0.01507	0.31253	.96
Body mass index, per 1 point	0.03822	0.02805	.07
Cardiac comorbidity [a]	−0.21588	0.27517	.43
Chronic obstructive lung disease	0.37357	0.34732	.28
CSA secondary to cardiac cause ± CSB [b]	0.07764	0.35395	.83
CSA secondary to opioids/multiple/other causes [b]	0.83313	0.41995	.05†
Full adherence to ASV at 1 month	0.07432	0.25932	.77
Outpatient visit rate pre-ASV versus post-ASV			
Age, per 1 year	0.16624	0.21121	.43
Male sex	−2.05913	6.31507	.74
Body mass index, per 1 point	0.23250	0.42126	.58
Cardiac comorbidity [a]	−1.18571	5.56012	.83
Chronic obstructive lung disease	−4.36181	7.01815	.53
CSA secondary to cardiac cause ± CSB [b]	11.13184	7.15197	.12
CSA secondary to opioids/multiple/other causes [b]	0.07907	8.47748	.99
Full adherence to ASV at 1 month	3.98118	5.24001	.45
Prescription medication rate pre-ASV versus post-ASV			
Age, per 1 year	1.37888	1.11192	.22
Male sex	−35.57446	48.45945	.47
Body mass index, per 1 point	1.11047	2.52419	.66
Cardiac comorbidity [a]	−21.84096	36.04819	.55
Chronic obstructive lung disease	−29.26414	56.72517	.61
CSA secondary to cardiac cause ± CSB [b]	75.43342	43.12043	.09
CSA secondary to opioids/multiple/other causes [b]	13.16106	82.04723	.87
Full adherence to ASV at 1 month	33.15261	34.64103	.34

* = change calculated as pre-ASV minus post-ASV. † = statistically significant value. Superscript letters indicate: a = coronary artery disease or atrial fibrillation, b = versus TECSA. ASV = adaptive servoventilation, CSA = central sleep apnea, CSB = Cheyne-Stokes breathing, TECSA = treatment-emergent central sleep apnea.

oxyhemoglobin saturation, smoking status, hypertension, AF, DM, stroke, COPD, antidepressant use and adherence to ASV at the time points closest to 1 month, 3 months and 1 year following commencement of the device were also not associated with change in the rate of EDV pre-ASV to post-ASV (all $P > .05$). None of these remained predictive in the multivariate analyses (**Table 4**).

Outpatient Visits Pre-ASV and Post-ASV

All 52 patients had at least one OPV noted pre-ASV as well as post-ASV. A total of 1,015 OPV were identified during 84.2 person-years pre-ASV and 1,112 OPV during 97.4 person-years post-ASV. The number of OPV per patient per year prior to ASV was 31.59 ± 112.42 and post-ASV was 13.60 ± 17.36, which was not statistically significant ($P = .22$).

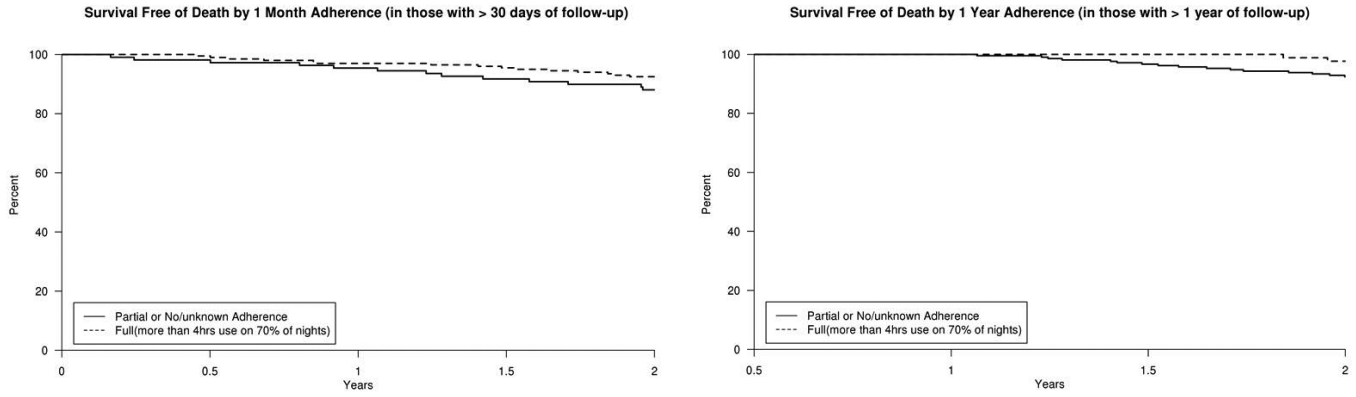
None of the patient factors (age, sex, BMI, AHI, OAI, CAI, minimum oxyhemoglobin saturation, smoking status, hypertension, CAD, HF, AF, DM, stroke, COPD, antidepressant use, CSA subtype and adherence to ASV at the time points closest to 1 month, 3 months and 1 year following commencement of the device) were associated with the rate of change of OPV pre-ASV to post-ASV in univariate

Table 5—Multivariate analysis for the outcome of death in those with > 365 days of follow-up (n = 289).

Variable	Hazard Ratio (CI)	*P*
Age, per 1 year	1.07 (1.04, 1.09)	< .01*
CSA secondary to cardiac cause ± CSB [a]	1.81 (1.09, 3.01)	.02*
CSA secondary to opioids/multiple/other [a]	1.75 (0.86, 3.55)	.12
Full adherence to ASV at 1 month [b]	0.56 (0.30, 1.05)	.07

* = statistically significant value. Superscript letters indicate: a = versus TECSA, b = versus partial/no/unknown adherence. ASV = adaptive servoventilation, CI = confidence intervals, CSA = central sleep apnea, CSB = Cheyne-Stokes breathing, SD = standard deviation, TECSA = treatment-emergent central sleep apnea.

Figure 2—Kaplan-Meier curves.



(A) Kaplan-Meier curves for survival free-of-death by adherence to ASV at 1 month (in patients with > 1 month of follow-up). **(B)** Kaplan-Meier curves for survival free-of-death by adherence to ASV at 1 year (in patients with > 365 days of follow-up). ASV = adaptive servoventilation.

analyses (all $P > .05$). Results of the multivariate analysis are shown in **Table 4**.

Prescription Medications Pre-ASV and Post-ASV

Of the 309 patients, 304 had at least one medication prescribed pre-ASV and 306 had at least one prescribed post-ASV, with 2 patients having no medication prescribed either pre-ASV or post-ASV. A total of 2,741 medications were identified pre-ASV and 2798 medications post-ASV during 534.0 and 594.1 person-years of follow-up respectively. The mean number of prescribed medications per patient per year pre-ASV was 6.68 ± 12.0 and post-ASV was 5.31 ± 5.86 ($P = .06$).

In univariate analyses, only stroke ($P = .01$) was associated with a change in the rate of medications used pre-ASV to post-ASV. Age, sex, BMI, AHI, OAI, CAI, minimum oxyhemoglobin saturation, smoking status, hypertension, CAD, HF, AF, DM, COPD, antidepressant us, CSA subtype and adherence to ASV at the time points closest to 1 month, 3 months and 1 year following commencement of the device were not associated with the rate of change of medications pre-ASV to post-ASV (all $P > .05$). Results of the multivariate analyses are shown in **Table 4**.

Mortality Post-ASV

A total of 91 (29.5%) patients died during follow-up. The primary cause of death in close to half the patients was noted to be cardiac or stroke-related. The remainder comprised respiratory, end-stage renal disease or neurologic disease-related and other miscellaneous causes of death. The overall 1-year and 2-year survival were 96.4% (95% CI 94.4–98.5) and 90.6% (95% CI 87.4–93.9), respectively. Two-year survival by CSA status was 92.4% (95% CI 89.0–95.9) among the TECSA, 93.6% (95% CI 85.3–100) in the "other" CSA, and 81.5% (95% CI 71.8–92.5) in the "cardiac-related" CSA categories.

Age, BMI, AHI, CAD, HF, COPD, diabetes mellitus, CSA secondary to cardiac causes (all $P < .05$) were associated with increased mortality, while full adherence to ASV at 1 year ($P = .03$) was associated with decreased risk of mortality in univariate analyses in the 298 patients with > 365 days of follow-up. Sex, smoking status, hypertension, AF, stroke, antidepressant use, other CSA subtypes and adherence to ASV at the time points closest to 1 month and 3 months following commencement of the device were not associated with mortality in univariate analyses in this group of patients. In multivariate analyses accounting for age, CSA subtype and full adherence to ASV at 1 month, only age was significantly associated with increased risk of death ($P < .01$) **Table 5**. The Kaplan-Meier estimates for survival in each of the groups divided based on adherence to the ASV device are depicted in **Figure 2**. No significant differences were noted between groups.

Usage and Efficacy of ASV in Patients Demonstrating Long-Term Adherence

To help determine continued usage and efficacy of the device in treating CSA in patients who were adherent to ASV, download data from the device was obtained from the electronic

medical record at the follow-up visit closest to the time point of 1 year following the commencement of ASV. Median nightly usage of ASV for this group of patients (n = 88) was 7:01 hours (range 4:00–10:54 hours). Mean residual AHI from the device (n = 75) was 4.1 events/h (SD 7.0 events/h) and median was 1.5 events/h (range 0–41 events/h). In patients in whom AHI was not available (not documented by the provider in the chart or could not be obtained from device) the treating provider did mention symptomatic benefit from the device at the clinic visit. Overnight oximetry on ASV was ordered in 3 of 4 patients in whom the residual AHI ≥ 15 events/h and showed that oxyhemoglobin saturation was well supported on the device in 2 patients (the test was not completed by 1 patient); in all of these patients the vast majority of events were observed to be in the form of hypopneas (apnea index < 5 events/h) on the download and there was excessive air leak noted in most cases. All of these patients (n = 88) were using first and second generation ResMed devices (mostly the ResMed S9 VPAP Adapt SV and a few were on the ResMed S7 VPAP Adapt SV, where the model was noted in the chart) except for two patients who were using previous generation Respironics devices. In addition to having a fixed expiratory positive airway pressure, the previous generation models of ResMed ASV may deliver excessive ventilation in some patients.[27]

Analyses of Outcomes After Removing Those With a Known EF of ≤ 45%

There was no change in the overall results of the analyses after removing those with a known cardiac EF of ≤ 45% (n = 85, 27.5% of the cohort); 88% of whom had a known diagnosis of HF pre-ASV or post-ASV) (**Table S1** in the supplemental material).

DISCUSSION

In this population-based cohort study mainly consisting of patients with TECSA, the use of ASV for CSA was not associated with a significant change in the rate of health care utilization when comparing the 2 years before and after starting therapy. Specifically, the rates of hospitalizations, EDV, OPV or prescription medication use after accounting for patient characteristics or CSA subtype, were unchanged. Additionally, adherence, partial adherence, or non-adherence to ASV therapy did not significantly alter health care utilization rates.

Our findings contrast with those evaluating the effects of treatment of OSA on health care utilization.[17–22] In case-control studies, patients with OSA treated with CPAP had a significant reduction in clinic visits compared with those remaining untreated, particularly in the 2 years after diagnosis of OSA compared to the 2 years prior to diagnosis.[20–22,28] Previous retrospective studies of people with OSA showed that adherence to positive airway pressure treatment was associated with lower rates of all hospitalizations as well as cardiovascular and pulmonary disease-related hospitalizations.[17–19]

Several factors might possibly explain why we did not find a significant effect on health care utilization, where it has been demonstrated in prior studies involving treatment of OSA. First, there were differing disease burdens experienced by patients in our cohort with CSA versus those with OSA reported in the literature. The proportion of patients with various medical comorbidities was relatively high in our cohort. The high mortality rate during follow-up indicates that a majority of these patients were very ill and that ASV may not have had a substantial impact in this context.

The rate of hospitalization and EDV in our study was more than double that in the United States general population aged ≥ 65 years between 2005–2014.[29,30] The rate of OPV per person per year prior to ASV in the sample in our study was more than ten times the rate of physician office visits per person in 2014 in the United States general population including all ages; this decreased post-ASV initiation, but the change was not statistically significant.[31] A report from the Center for Disease Control and Prevention reported that the majority (49%) of adults ≥ 65 years old were using 1–4 prescription medications and 42% were using ≥ 5 prescription medications in the last 30 days in 2013–2014.[32] In our cohort with a mean age of ≥ 65 years, 73% were using ≥ 5 prescription medications at baseline and there was a trend toward a decrease in the number of prescription medications per person from 7 to 5 following commencement of ASV which was not statistically significant. A previous 2-year longitudinal study of patients with OSA showed no significant difference in adherence to prescription medications in those adherent to CPAP compared to those that were nonadherent.[33]

The rates of hospitalization and other endpoints measured in our cohort of patients with CSA were higher than those noted in OSA populations. The study by Povitz et al. that examined patients with OSA who were chronically hypoxic, hospitalization rates before and after CPAP in the adherent group were 0.5 and 0.0 per person-year, while our cohort had rates of 0.7 and 0.8 per person-year prior to and following the use of ASV.[17] The rate of ED visits were 0.6 and 0.5 per person-year pre-CPAP and post-CPAP in the study by Povitz at al. versus 1.2 and 1.3 per person-year pre-ASV and post-ASV in our study. Similarly, the rates of hospitalization in other studies of patients with OSA were lower than that noted in our cohort.[18,19]

Not only were the patients in our study more ill, based upon their overall increased mortality, visit numbers, and prescription drug numbers, but the specific disease prevalence was likely different in our group compared with the prior populations studied in the OSA literature. The prevalence of cardiovascular disease in our population was at least 78%, while in Peker et. al., 57% of their population had cardiovascular disease.[18] Perhaps the population most resembling ours evaluated for health care utilization was that of Javaheri et al.[34] In that cohort of Medicare patients with new-onset HF who were diagnosed with sleep apnea, 74% were hospitalized during a 2-year observation period, and the cohort experienced annual mortality rates of 3.5% to 4.4%. In our group, 49% were hospitalized during the 2-year observation period, and our annual mortality rate was 3.6%. In Javaheri et al.'s cohort, treatment—which included all modalities—was associated with improved mortality. However, it is not known what proportion of those patients had CSA. Based upon prior studies, one might consider that over half of that cohort may have had CSA. No subgroup analysis was performed, so it is not known how treatment influenced the population of patients with HF and CSA. It should

be noted that TECSA was the most common indication for ASV in this study similar to that observed in a sleep center in the respiratory setting (80%) but lower than in the cardiology setting (41%) in the study by Malfertheiner et al.[35]

It is possible that without ASV we may have seen different results if patients were followed for a longer period of time, as was seen with health care utilization between the second to fifth year after a diagnosis of OSA in patients with coexisting ischemic heart disease.[21] To our knowledge, this is the only population-based study that examined all patients with CSA who were treated with ASV. One recent retrospective study showed an increased risk for hospital admission related to comorbid cardiovascular disorders in patients with CSA versus controls.[23] Thus far, there are no other studies evaluating the effects of ASV treatment for CSA on health care utilization.

The proportion of patients who died in our cohort that included patients with all CSA subtypes was high at 29.5% during the entire period of follow-up. Previous relatively large studies of patients with CSA and HF showed that a similar proportion (22% to 35%) of their cohorts died during a median follow-up period of 12–28 months and an increased rate of cardiac transplantation was also noted.[13,36,37] The literature regarding long-term mortality in other groups of patients with CSA is very limited.

In our sample there was a trend toward decreased mortality in patients with CSA who were fully adherent to ASV therapy at 1 year. While the overall number of patients on ASV was fairly large in our study, the number of patients in each adherence subcategory at the end of 1 year may have been insufficient to detect a significant difference. Sin et al. demonstrated a relative risk reduction in the combined death-transplantation rate in patients with HF and CSA/CSB who were adherent to CPAP.[38] A post-hoc analysis of the CANPAP trial data revealed a significant decrease in in the composite endpoint of death and transplant-free survival in patients whose CSA was suppressed by CPAP.[36,39] The recent SERVE-HF study, on the other hand, showed an increase in all-cause and cardiovascular mortality with ASV treatment in patients with CSA and HF with reduced EF at 12 months, contrary to expectation.[13] There was no change in the rate of unplanned hospitalizations for HF. We conducted analyses for each of the primary and secondary outcomes after removing all patients with a known EF of ≤ 45% which did not result in a change in the overall results.

Although the adherence rate to ASV was good at 1 month, suggesting that the therapy was well tolerated initially, usage appeared to decrease significantly with time in our study. The overall adherence rate appeared to be lower than expected for studies of positive airway pressure that have previously been conducted in this population, but it should be noted that these prior studies included patients with OSA and not CSA.[40,41]

In this study very few patients were diagnosed with a comorbidity post-ASV. Thus, for ease of the analyses, patients with (1) a particular comorbidity diagnosed pre-ASV or post-ASV, eg, hypertension, were compared against (2) those with no diagnosis of hypertension either pre-ASV or post-ASV. There was no change in the overall results when patients were categorized using the following three levels of comorbid classification instead of the two levels described above ie, (1) comorbid diagnosed pre-ASV, (2) comorbidity diagnosed post-ASV, and (3) no diagnosis either pre-ASV or post-ASV.

The strengths of this study include that it was a population-based cohort, thus we were able to study a complete population of patients with CSA who were treated with ASV, minimizing selection bias, independently collected data, and bias in evaluations of relationships of confounders to exposures and outcomes as well as other variables of interest. Other strengths include assessment of a relatively large cohort treated with ASV. In addition, we were able to thoroughly categorize subtypes of CSA, causes of hospitalization and death. Adherence to treatment was based on objective download data obtained from the ASV device. Follow-up data for at least 1 month after the prescription of ASV were available for the entire cohort.

There are some limitations of this study that need to be taken into account. This study has the inherent biases of a retrospective design. There may have been some patients who did not follow-up at the sleep center whose adherence was unknown but in fact may have been using ASV. However, the number of patients with unknown adherence was relatively small. Although compliance to medications was unknown, the number of medications prescribed (not used) was used as a surrogate marker of health care utilization in this study. Change in BMI post-ASV was not known but baseline BMI was not predictive of any of the outcomes and therefore is unlikely to have affected the results. Most patients with AF had paroxysmal AF; there may have been a few patients with AF or other cardiac comorbidity at the time of PSG with predominantly OSA at baseline who were included under the TECSA category using older definitions, but who may be classified under "cardiac-related" CSA using current terminology; however, this seems unlikely to have affected the overall results.[26] The influence of periodic limb movements and sleep fragmentation on outcomes was not accounted for in this study. There may have been other confounding factors such as cancer that were not accounted for in multivariate analyses, but examination of the primary cause of mortality suggested that this was not the case. Lastly, while the majority of patients had TECSA and we performed sub-analyses excluding those with a reduced EF, this was a heterogeneous clinical population of patients with CSA; thus, the results of this study may not be generalizable to all patients with CSA or in health systems with a different economic model such as those with a single payer.

In conclusion, our population-based study of patients on ASV treatment for CSA showed that although the therapy was well tolerated initially, there was no significant change in health care utilization, measured by hospitalizations, EDV, OPV or prescription medication use, in the 2 years following commencement of the device compared to the 2 years prior to the use of the device, after accounting for multiple confounders. The high mortality rate likely reflects the increased comorbidity burden and overall ill health of this population.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
AHI, apnea-hypopnea index

ASV, adaptive servoventilation
BMI, body mass index
CAD, coronary artery disease
CAI, central apnea index
COPD, chronic obstructive pulmonary disease
CPAP, continuous positive airway pressure
CSA, central sleep apnea
CSB, Cheyne Stokes breathing
DM, diabetes mellitus
EDV, emergency department visits
EF, ejection fraction
HF, heart failure
OAI, obstructive apnea index
OPV, outpatient visits
PSG, polysomnography
REP, Rochester Epidemiology Project
TECSA, treatment-emergent central sleep apnea

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