OBSTRUCTIVE SLEEP APNEA

ORIGINAL RESEARCH

In-hospital Outcomes and Arrhythmia Burden in Patients with Obstructive Sleep Apnea and Heart Failure with Preserved Ejection Fraction

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ABSTRACT. Patients with obstructive sleep apnea (OSA) have an increased risk for arrhythmias compared to patients without OSA. However, data quantifying the risk of inpatient complications in patients with heart failure with preserved ejection fraction (HFpEF) are lacking. We sought to compare inpatient outcomes and the occurrence of arrhythmias in patients with HFpEF with and without OSA, respectively. Furthermore, we compared the prevalence of arrhythmias with nocturnal continuous positive airway pressure (CPAP) therapy. We performed a retrospective study using the National Inpatient Sample from 2016–2018 to identify patients with HFpEF with and without OSA. Propensity score matching, adjusting for age, gender, race, hospital characteristics, income, and comorbidities, was used to select matched samples between both groups. From 2016–2018, 127,773 hospitalizations with HFpEF were identified; among these patients, 20% had OSA. Nocturnal CPAP was utilized in 9% of these patients. Patients with OSA had a higher mortality rate, a longer duration of hospitalization, and greater medical costs. In addition, OSA was associated with higher incidence rates of atrial fibrillation, atrial flutter, premature depolarization, sick sinus syndrome, ventricular tachycardia, and atrioventricular block. Nocturnal CPAP was not associated with a lower arrhythmia incidence; however, there was a non-significant trend toward a lower cardiac arrest incidence. In conclusion, OSA in patients with HFpEF was associated with greater mortality, longer hospitalization stays, and higher medical costs relative to findings in patients without OSA. Furthermore, OSA was associated with tachyarrhythmias and bradyarrhythmias in HFpEF patients. Nocturnal CPAP was only utilized in 9% of patients, with no difference in arrhythmogenesis.

KEYWORDS. Atrial fibrillation, diastolic heart failure, heart block, sick sinus syndrome, sleep-disordered breathing.

Introduction

Heart failure with preserved ejection fraction (HFpEF) represents approximately half of all heart failure diagnoses worldwide, and its prevalence is increasing annually.1,2 Moreover, it is estimated that approximately 30% of men and 15% of women meet the diagnostic criteria for obstructive sleep apnea (OSA) in North America.3,4 Heart failure and OSA have considerable overlap as observational studies have shown that OSA is present in roughly 50% of HFpEF patients.5 OSA is characterized by recurrent intermittent upper-airway obstructive events, leading to hypoxemia, hypercapnia, and autonomic dysregulation.6 OSA has been
associated with sudden cardiac death and a broad spectrum of cardiac rhythm disorders, with the most evidence being available for atrial fibrillation. However, the prevalence of arrhythmias in HFpEF patients with OSA has not been definitively established. Furthermore, studies have demonstrated a reduced atrial fibrillation burden with continuous positive airway pressure (CPAP) therapy. The data regarding CPAP therapy with other arrhythmias are preliminary but point toward reduced incidence rates of bradyarrhythmia, ventricular ectopy, and sudden cardiac death. However, there is a paucity of data from heart failure patients.

The purpose of this study was to compare the prevalence of cardiac arrhythmias in HFpEF patients with and without OSA, utilizing the National Inpatient Sample (NIS) database from 2016–2018. In addition, we sought to compare in-hospital mortality rates, the length of hospitalization, and medical costs of hospitalization among these patients. Finally, we examined the utilization of inpatient nocturnal CPAP in patients with OSA to assess whether the incidence of arrhythmias was decreased in these patients compared to patients who did not receive nocturnal CPAP.

Methods

Data source

The data for this study were drawn from the NIS database, the Healthcare Cost and Utilization Project, and the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest collection of all-payer data on inpatient hospitalizations in the United States. The dataset represents an approximated 20% stratified sample of all inpatient discharges from U.S. hospitals. The database provides de-identified information for each hospitalization. This information includes patient-level and hospital-level factors, such as patient demographic characteristics, primary and secondary diagnoses and procedures, AHRQ comorbidities, length of stay, hospital characteristics, and costs of hospitalization. National estimates can be calculated using the patient-level and hospital-level sampling weights that the NIS provides. For this study, data were obtained from the years 2016–2018.

Study population and variables

The International Classification of Diseases, 10th revision (ICD-10), was used to report diagnoses and procedures in the NIS database. We identified patients hospitalized with HFpEF (ICD-10–Clinical Modification [CM] codes I530, I5031, I5032 and I5033) and OSA (ICD-10–CM code G473). We excluded patients aged <18 years, those with a body mass index (BMI) of <29.9 kg/m², and those with a pacemaker or an implantable cardioverter-defibrillator. Of the patients with HFpEF and OSA, patients who utilized nocturnal CPAP (ICD-10 Procedure Coding System code 5A09357) were also identified. In order to mitigate selection bias and control for patient and institutional imbalances, propensity scoring was used to select matched samples of HFpEF patients with OSA and those without OSA. The scoring was based on a multivariate logistic regression model, accounting for age, gender, race, hospital type, hospital region, hospital teaching status, median household income, and medical comorbidities (cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes, hypertension, obesity, peripheral vascular disease, smoking, and valvular heart disease). Using 8- to 1-digit matching, we paired each diastolic heart failure admission with OSA with an admission without OSA.

Study outcomes

The primary analysis of this study was a comparison of in-hospital mortality, length of hospitalization, and medical cost of hospitalization between HFpEF patients with OSA and those without OSA. The secondary analysis compared the prevalence of arrhythmias, including atrial fibrillation, atrial flutter, atrioventricular block, cardiac arrest, premature depolarization (atrial, ventricular, and junctional), sick sinus syndrome, supraventricular tachycardia (SVT), ventricular tachycardia, and ventricular fibrillation, in these patients. A subgroup analysis was also conducted in patients with HFpEF and OSA, comparing the incidence of these arrhythmias in those with and without inpatient nocturnal CPAP.

Statistical analyses

All statistical analysis was performed using SAS Survey Procedures (SAS version 9.4; SAS Institute Inc., Cary, NC, USA). Statistical significance was defined by a 2-sided test with \( P < .05 \). The national estimates were calculated after accounting for the sample design elements (clusters, strata, and trend weights) provided by the NIS. Continuous variables were reported as weighted mean ± standard deviation (SD) values, and categorical variables were reported as weighted numbers (n) and percentages (%). The SDs of weighted means were estimated using the Taylor linearization method that incorporated the sample design. The Rao–Scott-modified chi-squared test was used to test the distribution difference for categorical variables, while a weighted Student’s t-test was used to analyze the normally distributed continuous variables. Variables that were not normally distributed were tested using the Wilcoxon rank-sum test. Multivariate logistic regression was used to estimate the odds ratio of in-hospital mortality and several outcomes after adjusting for patient demographics, hospital type, hospital region, hospital teaching status, median household income, and medical comorbidities.

Results

Population characteristics and comorbidities

The design of this study is presented in the flowchart in Figure 1. From 2016–2018, we identified a total of 127,773
unweighted hospitalizations with HFpEF; of these patients, 25,529 (20%) also had OSA. After applying propensity scores, nocturnal CPAP was utilized in 2,250 (9%) of these patients. Demographic and baseline characteristics of these patients before and after applying propensity matching are presented in Table 1. The mean age of the patients with HFpEF and OSA was 70 years, while that of those without OSA was 76 years. Of the patients with HFpEF, OSA was seen at similar rates in men (50%) and women (50%); however, in patients without OSA, there was a predominance of women (62%) with OSA. The racial distribution in patients with HFpEF and OSA was 73% Caucasian, 17% African American, 6.3% Hispanic, 1.1% Asian, 0.4% Native American, and 1.7% unspecified. The majority of patients were equally distributed in both groups; however, there was a trend toward an increased number of African Americans among patients with OSA. In patients with HFpEF and OSA, there were increased rates of chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes, and obesity. Patients without OSA had a higher frequency of cerebrovascular disease, peripheral vascular disease, and valvular heart disease. Both groups had a similar prevalence of hypertension and smoking.

In-hospital Outcomes and Arrhythmia Burden in Patients with OSA and HFpEF

The multivariate logistic regression analysis results comparing outcomes in patients with HFpEF with and without OSA are presented in Table 2. The results of the primary analysis indicated that patients with OSA had increased mortality (odds ratio [OR], 1.33; 95% confidence interval [CI], 1.28–1.37; \( P < .001 \)), longer length of hospitalization (5.6 vs. 5.3 days; \( P < .001 \)), and increased medical costs of hospitalization ($61,844 vs. $56,182; \( P < .001 \)) compared to patients without OSA. The secondary analysis was a comparison of the prevalence of arrhythmias in both groups. Patients with HFpEF and OSA had a higher prevalence of atrial fibrillation (OR, 1.29; 95% CI, 1.27–1.31; \( P < .001 \)), atrial flutter (OR, 1.13; 95% CI, 1.09–1.17; \( P < .001 \)), premature depolarization (OR, 1.08; 95% CI, 1.01–1.15; \( P < .02 \)), sick sinus syndrome (OR, 1.2; 95% CI, 1.12–1.29; \( P < .001 \)), SVT (OR, 1.07; 95% CI, 1.02–1.13; \( P < .02 \)), ventricular tachycardia (OR, 1.19; 95% CI, 1.13–1.24; \( P < .001 \)), first-degree atrioventricular block (OR, 1.17; 95% CI, 1.09–1.25; \( P < .002 \)), and third-degree atrioventricular block (OR, 1.16; 95% CI, 1.01–1.33; \( P < .03 \)). We also performed a subgroup analysis, comparing the occurrence of arrhythmias with
the utilization of inpatient nocturnal CPAP in patients with HFpEF and OSA. The results of this analysis are presented in Table 3. Our analysis showed that nocturnal CPAP is not associated with a change in arrhythmia prevalence in the inpatient setting. However, there was a non-significant trend toward a decreased likelihood of cardiac arrest in patients who utilized nocturnal CPAP (0.7% vs. 1.3%; \( P = .06 \)).

Table 3: Baseline Characteristics for Patients in the Unmatched and Matched Cohorts

|                        | Unmatched Cohort | Matched Cohort |
|------------------------|------------------|----------------|
|                        | HFrEF with OSA   | HFrEF Without OSA | HFrEF with OSA | HFrEF Without OSA |
| n (unweighted)         | 25,529           | 102,244         | 24,318         | 24,318             |
| n (weighted)           | 127,645          | 511,220         | 121,590        | 121,590            |
| Mean (SD)              | 69.8 (0.1)       | 75.8 (0.1)      | .001           | 69.9 (0.1)         | 69.7 (0.1) | .102 |
| Gender                 |                  |                | Weighted n (%) |                  | Weighted n (%) |
| Male                   | 63,290 (50)      | 193,145 (38)   | .001           | 59,435 (49)        | 58,670 (48) | .17 |
| Female                 | 64,355 (50)      | 318,075 (62)   |                | 62,155 (51)        | 62,920 (52) |
| Race                   |                  |                | Age, years     |                  | Mean (SD) |
| Caucasian              | 91,765 (73)      | 368,645 (73)   | .59            | 89,145 (73)        | 89,650 (73) |
| African American       | 21,310 (17)      | 68,640 (14)    |                | 20,710 (17)        | 20,745 (17) |
| Hispanic               | 7,910 (6)        | 39,845 (8)     | .001           | 7,750 (6)          | 7,485 (6)  |
| Asian                  | 1,425 (1)        | 11,655 (2)     |                | 1,405 (1)          | 1,225 (1)  |
| Native American        | 520 (0.4)        | 2,260 (0.4)    |                | 505 (0.4)          | 530 (0.4)  |
| Other                  | 2,100 (2)        | 11,860 (2)     |                | 2,075 (1.7)        | 1,955 (1.6) |
| Hospital teaching status |                |                | Weighted n (%) |                  | Weighted n (%) |
| Rural                  | 1,225 (10)       | 55,170 (11)    | .17            | 11,420 (9)         | 112 (9)    |
| Urban non-teaching     | 25,835 (20)      | 114,915 (23)   | .001           | 24,915 (20)        | 23,860 (20) |
| Urban teaching         | 89,560 (70)      | 341,145 (67)   |                | 85,255 (70)        | 86,455 (71) |
| Hospital bed size      |                  |                | Median income  |                  | Mean (SD) |
| Small                  | 25,655 (20)      | 112,220 (22)   | .005           | 36,110 (30)        | 35,770 (30) | .91 |
| Medium                 | 39,365 (31)      | 160,755 (31)   |                | 33,130 (27)        | 33,200 (27) | .40 |
| Large                  | 62,630 (49)      | 238,255 (47)   |                | 59,275 (49)        | 60,290 (50) |
| Median income          | $1–$45,999       | 37,065 (29)    | .005           | 36,110 (30)        | 35,770 (30) | .91 |
| $46,000–$58,999        | 34,640 (28)      | 137,170 (27)   |                | 33,130 (27)        | 33,200 (27) | .40 |
| $59,000–$78,999        | 30,360 (24)      | 120,750 (24)   |                | 29,185 (24)        | 29,170 (24) |
| $79,000+              | 23,800 (19)      | 102,295 (20)   |                | 23,165 (19)        | 23,450 (19) |
| Comorbidities (%)      |                  |                | Coroventricular disease | 3,015 (2) | 15,880 (3) | .001 | 2,880 (2) | 2,720 (2) | .36 |
| Chronic kidney disease | 63,970 (50)      | 233,240 (46)   | .001           | 60,890 (50)        | 60,590 (50) | .59 |
| Chronic obstructive pulmonary disease | 56,215 (44) | 162,555 (32) | .001           | 52,940 (43)        | 52,300 (43) | .27 |
| Coronary artery disease | 59,880 (47)      | 219,230 (43)   | .001           | 56,775 (47)        | 56,545 (47) | .69 |
| Diabetes               | 76,240 (60)      | 221,935 (43)   | .001           | 72,215 (59)        | 72,445 (60) | .67 |
| Hypertension           | 79,490 (62)      | 319,080 (62)   | .70            | 75,735 (62)        | 76,675 (63) | .09 |
| Obesity                | 73,895 (58)      | 11,355 (22)    | .001           | 69,700 (57)        | 69,125 (57) | .32 |
| Peripheral vascular disease | 12,270 (10) | 55,900 (11)    | .001           | 11,690 (10)        | 11,240 (9)  | .17 |
| Smoking                | 13,535 (11)      | 52,775 (10)    | .22            | 13,005 (11)        | 12,705 (10) | .39 |
| Valvular heart disease | 28,050 (22)      | 135,805 (27)   | .001           | 26,850 (22)        | 25,880 (21) | .04 |

Abbreviations: HFpEF, heart failure with preserved ejection fraction; OSA, obstructive sleep apnea; SD, standard deviation.

Discussion

This propensity-matched, retrospective study drew data from the 2016–2018 NIS, the largest all-payer inpatient database in the U.S., to compare adverse clinical outcomes in HFrEF patients with and without OSA. The principal findings of this study were as follows: (1) OSA was associated with increased in-hospital
Table 2: In-hospital Outcomes in the Matched and Unmatched Cohorts

|                                      | Unmatched Cohort | Matched Cohort |
|--------------------------------------|------------------|----------------|
|                                      | HFP EF with OSA  | HFP EF Without OSA | HFP EF with OSA  | HFP EF Without OSA |
| Length of hospitalization, days      | Mean (SD)        | Mean (SD)        | P Value          | Mean (SD)        | Mean (SD)        | P Value          |
| Medical cost of hospitalization      | $56,556 (838)    | $56,220 (855)    | <0.001*          | $61,844 (982)    | $56,182 (865)    | <0.001*          |
|                                      | Weighted n (%)   | Weighted n (%)   | P Value          | Weighted n (%)   | Weighted n (%)   | Odds Ratio (95% CI); P Value |
| In-hospital mortality                | 10,775 (2.1)     | 1,510 (1.2)     | <0.001*          | 2,095 (1.7)     | 1,405 (1.2)     | 1.33 (1.28–1.37); <0.001* |
| Atrial fibrillation                  | 62,760 (49.2)    | 248,625 (48.6)  | 0.161            | 60,120 (49.4)   | 52,485 (43.2)   | 1.29 (1.27–1.31); <0.001* |
| Atrial flutter                       | 6,715 (5.3)      | 22,215 (4.3)    | <0.001*          | 6,425 (5.3)     | 5,735 (4.7)     | 1.13 (1.09–1.17); <0.001* |
| Cardiac arrest                       | 1,060 (0.8)      | 3,980 (8)       | 0.423            | 990 (0.8)       | 1,020 (0.8)     | 0.97 (0.89–1.06); 0.502 |
| Premature depolarization             | 2,000 (1.6)      | 7,390 (1.4)     | 0.152            | 1,910 (1.6)     | 1,770 (1.5)     | 1.08 (1.01–1.15); 0.02*  |
| Sick sinus syndrome                  | 1,770 (1.4)      | 7,810 (1.5)     | 0.088            | 1,715 (1.4)     | 1,435 (1.2)     | 1.2 (1.12–1.29); <0.001* |
| Supraventricular tachycardia         | 10,070 (2.0)     | 2,340 (1.8)     | 0.135            | 2,420 (2.0)     | 2,265 (1.9)     | 1.07 (1.02–1.13); 0.022* |
| Ventricular tachycardia              | 1,650 (1.3)      | 7,610 (1.5)     | 0.016*           | 1,910 (1.6)     | 1,545 (1.3)     | 1.19 (1.13–1.24); <0.001* |
| Ventricular fibrillation             | 180 (0.1)        | 710 (.1)        | 0.935            | 205 (0.2)       | 170 (0.1)       | 1.17 (1.02–1.36); 0.071 |
| First-degree AV block                | 1,795 (1.4)      | 6,405 (1.3)     | 0.056            | 1,690 (1.4)     | 1,580 (1.3)     | 1.17 (1.09–1.25); 0.002* |
| Second-degree AV block               | 655 (0.5)        | 2,250 (4.4)     | 0.136            | 600 (0.5)       | 590 (0.5)       | 1.02 (0.91–1.14); 0.771 |
| Third-degree AV block                | 460 (0.4)        | 2,135 (4.4)     | 0.170            | 435 (0.4)       | 375 (0.3)       | 1.16 (1.01–1.33); 0.03*  |

Abbreviations: AV, atrioventricular; CI, confidence interval; HFP EF, heart failure with preserved ejection fraction; OSA, obstructive sleep apnea; SD, standard deviation. *Statistically significant.

Table 3: In-hospital Outcomes in Patients with and Without Nocturnal Continuous Positive Airway Pressure

|                                      | Unmatched Cohort | Matched Cohort |
|--------------------------------------|------------------|----------------|
|                                      | HFP EF with OSA  | HFP EF Without OSA | HFP EF with OSA  | HFP EF Without OSA |
| n (unweighted)                       | 2,250            | 2,250           | 2,250            | 2,250 |
| n (weighted)                         | 11,250           | 11,250          | 11,250           | 11,250 |
| Weighted n (%)                       | Weighted n (%)   | Weighted n (%)   | P Value          | Weighted n (%)   | Weighted n (%)   | Odds Ratio (95% CI); P Value |
| Atrial fibrillation                  | 2,155 (19.2)     | 2,155 (19.2)    | 0.185            | 2,155 (19.2)    | 2,135 (19)      | .879 |
| Atrial flutter                       | 670 (6)          | 670 (6)         | 0.204            | 670 (6)         | 570 (5.1)       | .236 |
| Cardiac arrest                       | 150 (1.3)        | 840 (0.8)       | 0.024            | 79 (0.7)        | 150 (1.3)       | .063 |
| Premature depolarization             | 225 (2)          | 1,685 (1.5)     | 0.136            | 225 (2)         | 150 (1.3)       | .090 |
| Supraventricular tachycardia         | 245 (2.2)        | 2,020 (1.8)     | 0.274            | 245 (2.2)       | 230 (2)         | .751 |
| Ventricular tachycardia              | 160 (1.4)        | 1,385 (1.3)     | 0.514            | 160 (1.4)       | 135 (1.2)       | .412 |
| Ventricular fibrillation             | 25 (0.2)         | 145 (0.1)       | 0.371            | 25 (0.2)        | 0 (0)           | NA |
| First-degree AV block                | 195 (1.7)        | 1,495 (1.4)     | 0.224            | 195 (1.7)       | 185 (1.6)       | .824 |
| Second-degree AV block               | 60 (0.5)         | 540 (0.5)       | 0.799            | 60 (0.5)        | 35 (0.3)        | .273 |
| Third-degree AV block                | 30 (0.3)         | 405 (0.4)       | 0.379            | 30 (0.3)        | 60 (0.5)        | .176 |

Abbreviations: AV, atrioventricular; CI, confidence interval; HFP EF, heart failure with preserved ejection fraction; NA, not available; OSA, obstructive sleep apnea; SD, standard deviation.

mortality, a longer duration of hospitalization, and increased medical costs of hospitalization; (2) OSA was associated with an increased prevalence of atrial fibrillation, atrial flutter, premature depolarization, sick sinus syndrome, SVT, ventricular tachycardia, first-degree atrioventricular block, and third-degree atrioventricular block; and (3) the utilization of inpatient nocturnal CPAP was not associated with a reduced prevalence of arrhythmia.

This study demonstrated that 20% of patients with HFP EF had OSA, consistent with previous reports showing an average prevalence of 23% in men and women in the general population. However, these results were considerably lower than those reported in smaller observational studies, as OSA has been seen in up to 50% of heart failure patients. In agreement with previous reports, OSA was more common in men, those with increased BMI, and those with multiple cardiovascular comorbidities.
Furthermore, previous studies assessing chronic heart failure patients with long-term follow-up have shown OSA to be associated with increased mortality.\textsuperscript{25,26} Moreover, a similar study to the present one utilizing the NIS identified pulmonary hypertension as a strong independent predictor of in-hospital mortality; although OSA was not specifically assessed,\textsuperscript{27} there is considerable overlap in these patient populations.\textsuperscript{31,32}

Several pathophysiological mechanisms contribute to the increased mortality and arrhythmogenesis in heart failure patients with OSA. Periods of intermittent hypoxia in OSA result in oxidative stress to cardiac tissues, resulting in impaired energy metabolism and the generation of pro-inflammatory cytokines and reactive oxygen species (ROS).\textsuperscript{33} Furthermore, OSA results in tissue remodeling, inflammation, and autonomic imbalance.\textsuperscript{34} Heart failure in itself is an independent enhancer of ROS production,\textsuperscript{35} tissue remodeling,\textsuperscript{36} inflammation,\textsuperscript{37} and autonomic imbalance,\textsuperscript{38} thereby increasing the propensity for arrhythmogenesis in OSA patients. Autonomic imbalances in OSA are caused by negative thoracic pressure during periods of hypopnea, resulting in alternations in baroreceptor and chemoreceptor reflexes.\textsuperscript{39} These derangements can favor either profound vagal activity, leading to bradyarrhythmia, or sympathetic activation favoring tachyarrhythmias.\textsuperscript{40} This cascade deranges cardiomyocyte ion exchange through action on sodium channels, potassium channels, and gap junction proteins, generating inappropriate action potentials and triggering arrhythmia.\textsuperscript{41,43}

Our study found that atrial fibrillation was present in 49% of the patients with HFrEF and OSA, with statistically significant increased odds compared to patients without OSA. While not as common as atrial fibrillation, other tachyarrhythmias, such as atrial flutter, premature depolarization, SVT, and ventricular tachycardia were also more common in patients with OSA. Although not specifically considering HFrEF patients, studies of OSA patients have reported an increased likelihood of tachyarrhythmias.\textsuperscript{14,44,45} Furthermore, OSA is a predictor of the incidence of atrial fibrillation\textsuperscript{46} and its recurrence after cardioversion.\textsuperscript{16} There is a paucity of data regarding atrial flutter. Studies have reported a higher prevalence of atrial flutter in patients with central sleep apnea and Cheyne–Stokes breathing but not so with OSA.\textsuperscript{14,47} Our study also found a higher prevalence of bradyarrhythmias with OSA in HFrEF patients, including sick sinus syndrome, first-degree atrioventricular block, and third-degree atrioventricular block. While not studied in HFrEF patients, studies have commonly documented long pauses with sinus arrest or complete heart block occurring in OSA patients during sleep.\textsuperscript{11,13,46} Interestingly, in 80% of OSA patients with atrioventricular block, sinus node function was normal on electrophysiologic study and reversible with atropine, suggesting normal conduction anatomy in these patients.\textsuperscript{49} Moreover, OSA is 10 times more prevalent in sick sinus syndrome patients compared to the general population.\textsuperscript{50}

A subgroup analysis in patients with HFrEF and OSA identified that only 9% of patients had inpatient nocturnal CPAP utilized. We also found that CPAP was not associated with a difference in cardiac conduction disorders; however, there was a non-significant trend toward a decrease in cardiac arrest. Multiple studies have demonstrated the benefits of CPAP in OSA patients in reducing tachyarrhythmias\textsuperscript{51,52} and bradyarrhythmias.\textsuperscript{11,48,53} In addition, CPAP therapy has been shown to improve heart rate variability and baroreflex sensitivity in heart failure patients, thus enhancing vagal modulation and autonomic nervous system regulation.\textsuperscript{54,55} However, there is a paucity of studies assessing the prevalence of arrhythmia in heart failure patients treated with CPAP. One study reported a 59% decrease in the frequency of premature ventricular depolarization.\textsuperscript{39} We hypothesize that no benefit was found with arrhythmia prevalence in our patients because the benefits of CPAP are typically seen with long-term compliance rather than in the short term. However, the trend toward decreased cardiac arrest with CPAP is promising and may signal the potential for short-term benefits of inpatient therapy.

The limitations of this study include the inherent deficiencies of national registry analyses; the NIS is an administrative database susceptible to documentation errors, coding errors, and misdiagnoses. Discharge-level coding relies on individual institutions; therefore, results may not be consistent across various centers. There was likely a degree of misclassification as some patients may have had undiagnosed OSA and were potentially allocated to the incorrect group. In addition, the pathogenesis of bradyarrhythmia with OSA involves vagotonia; therefore, it was anticipated that OSA treatment with CPAP would reduce vagotonia, thus decreasing the arrhythmia risk. However, no difference was detected, indicating a high likelihood for miscategorized OSA status in the NIS database. In addition, our results were likely subject to confounding factors indiscernible by the NIS database, such as New York Heart Association (NYHA) functional classification, grade of diastolic dysfunction, and OSA severity. Specifically, in patients with HFrEF, the diastolic dysfunction grade correlates with increased apnea–hypopnea index, conferring a worse disease burden.\textsuperscript{56} Furthermore, although not assessed in patients with OSA, worsening NYHA functional class has been established as a cause of increased mortality in heart failure patients.\textsuperscript{57,58} Therefore, future prospective studies should categorize patients based on disease severity. Moreover, the NIS cannot capture readmissions; accordingly, there is likely a degree of duplicated data as patients with heart failure have an estimated 30% readmission rate within 90 days.\textsuperscript{59}

Conclusion

The present study demonstrated that OSA in HFrEF patients was associated with increased in-hospital mortality, length of hospitalization, and increased medical costs compared to those without OSA. Furthermore, this analysis showed that OSA in HFrEF patients was associated with an increased likelihood of atrial fibrillation, atrial flutter, premature depolarization, sick sinus
syndrome, SVT, ventricular tachycardia, and atrioventricular block. These results were consistent with previous reports in OSA patients without heart failure; however, future studies of heart failure patients with reduced and preserved ejection fraction, respectively, are needed. Furthermore, the use of nocturnal CPAP in these patients was not associated with decreased arrhythmias, although it was only utilized in 9% of patients. However, we found a non-significant trend toward decreased cardiac arrest in patients treated with CPAP, implying a possible benefit of inpatient CPAP.

References

1. Gladden JD, Linke WA, Redfield MM. Heart failure with preserved ejection fraction. Pflugers Arch. 2014;466(6):1037–1053.
2. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. 2011;123(18):2006–2013.
3. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort Study. WMJ. 2009;108(5):246–249.
4. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177(9):1006–1014.
5. Herrscher TE, Akre H, Overland B, Sandvik L, Westheim AS. High prevalence of sleep apnea in heart failure outpatients: even in patients with preserved systolic function. J Card Fail. 2011;17(5):420–425.
6. Yeghiazarians Y, Niece H, Tietjens JR, et al. Obstructive sleep apnea and cardiovascular disease a scientific statement from the American Heart Association. Circulation. 2021;144(3):e56–e67.
7. Gami AS, Olson EJ, Shen WK, et al. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. J Am Coll Cardiol. 2013;62(7):610–616.
8. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med. 2005;352(12):1206–1214.
9. Tavares L, Lador A, Valderrabano M. Sleep apnea and atrial fibrillation: role of the cardiac autonomic nervous system. Methodist Debakey Cardiovasc J. 2021;17(1):49–52.
10. Patel N, Donahue C, Shenoy A, Patel A, El-Shereif N. Obstructive sleep apnea and arrhythmia: a systemic review. Int J Cardiol. 2017;228:967–970.
11. Simantirakis EN, Schiza SI, Marketou ME, et al. Severe bradycardia in patients with sleep apnea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder. Eur Heart J. 2004;25(12):1070–1076.
12. Flemons WW, Remmers JE, Gillis AM. Sleep apnea and cardiac arrhythmias. Is there a relationship? Am Rev Respir Dis. 1993;148(3):618–621.
13. Becker HF, Koehler U, Stammnitz A, Peter JH. Heart block in patients with sleep apnoea. Thorax. 1998;53(Suppl 3):S29–S32.
14. Mehra R, Stone KL, Varosy PD, et al. Nocturnal arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. Arch Intern Med. 2009;169(12):1147–1155.
15. Raghuram A, Clay R, Kumbam A, Tereshchenko LG, Khan A. A systematic review of the association between obstructive sleep apnea and ventricular arrhythmias. J Clin Sleep Med. 2014;10(10):1155–1160.
16. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation. 2003;107(20):2589–2594.
17. Naruse Y, Tada H, Satoh M, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm. 2013;10(3):331–337.
18. Holmquist F, Guan N, Zhu Z, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation—results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J. 2015;169(5):647–654.e2.
19. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnea. Thorax. 2005;60(9):781–785.
20. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. Chest. 2005;127(6):2076–2084.
21. Houchens RL, Ross D EA. HCUP Methods Series Using the HCUP National Inpatient Sample to Estimate Trends (Revised 12/15/15) Report # 2006-05. Available at: http://www.hcup-us.ahrq.gov. Accessed July 5, 2021.
22. Bitter T, Faber L, Hering D, Langer C, Horstkotte D, Oldenburg O. Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. Eur J Heart Fail. 2009;11(6):602–608.
23. Chan J, Sanderson J, Chan W, et al. Prevalence of sleep-disordered breathing in diastolic heart failure. Chest. 1997;111(6):1488–1493.
24. Kasai T, Bradley TD. Obstructive sleep apnea and heart failure: pathophysiologic and therapeutic implications. J Am Coll Cardiol. 2011;57(2):119–127.
25. Abdullah A, Eigbire G, Salama A, Wahab A, Nadkarni N, Alweis R. Relation of obstructive sleep apnea to risk of hospitalization in patients with heart failure and preserved ejection fraction from the national inpatient sample. Am J Cardiol. 2018;122(4):612–615.
26. Mentz RJ, Kelly JP, von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol. 2014;64(21):2281–2293.
27. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med. 1999;160(4):1101–1106.
28. Khayat R, Jarjoura D, Porter K, et al. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. Eur Heart J. 2015;36(23):1463–1469.
29. Damy T, Margarit L, Noroc A, et al. Prognostic impact of sleep-disordered breathing and its treatment with nocturnal ventilation for chronic heart failure. Eur J Heart Fail. 2012;14(9):1009–1019.
30. Goyal P, Almarzooq ZI, Horn EM, et al. Characteristics of hospitalizations for heart failure with preserved ejection fraction. Am J Med. 2016;129(6):635.e15–635.e26.
31. Ismail K, Roberts K, Manning P, Manley C, Hill NS. OSA and pulmonary hypertension: time for a new look. Chest. 2015;147(3):847–861.
32. Minai OA, Ricartte B, Kaw R, et al. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am J Cardiol. 2009;104(9):1300–1306.
33. May AM, Mehra R. Obstructive sleep apnea: role of intermittent hypoxia and inflammation. *Semin Respir Crit Care Med*. 2014;35(5):531–544.

34. Chadda KR, Fazmin IT, Ahmad S, et al. Arrhythmogenic mechanisms of obstructive sleep apnea in heart failure patients. *Sleep*. 2018;41(9):1–14.

35. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. *Am J Physiol Heart Circ Physiol*. 2011;301(6):2181–2190.

36. Nikolaidou T, Cai XJ, Stephenson RS, et al. Congestive heart failure leads to prolongation of the pr interval and atrioventricular junction enlargement and ion channel remodelling in the rabbit. *PLoS One*. 2015;10(10):e0141452.

37. Askevold ET, Gulledstad L, Dahl CP, Yndestad A, Ueland T, Aukrust P. Interleukin-6 signaling, soluble glycoprotein 130, and inflammation in heart failure. *Curr Heart Fail Rep*. 2014;11(2):146–155.

38. Smith RP, Veale D, Pépin JL, Lévy PA. Obstructive sleep apnea and the autonomic nervous system. *Sleep Med*. 1998;2(2):69–92.

39. Leung RST. Sleep-disordered breathing: autonomic mechanisms and arrhythmias. *Prog Cardiovasc Dis*. 2009;51(4):324–338.

40. Jeong EM, Liu M, Sturdy M, et al. Metabolic stress, reactive oxygen species, and arrhythmia. *J Mol Cell Cardiol*. 2012;52(2):454–463.

41. Köhler AC, Sag CM, Maier LS. Reactive oxygen species and arrhythmias. *Prog Cardiovasc Dis*. 2014;73:92–102.

42. Kozhevnikov DO, Yamamoto K, Robotis D, Restivo M, El-Sherif N. Electrophysiological mechanism of enhanced susceptibility of hypertrophied heart to acquired torsade de pointes arrhythmias: tridimensional mapping of activation and recovery patterns. *Circulation*. 2002;105(9):1128–1134.

43. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2006;173(8):910–916.

44. Gilman MP, Floras JS, Usui K, Kaneko Y, Leung RST, Bradley TD. Continuous positive airway pressure increases heart rate variability in heart failure patients with obstructive sleep apnoea. *Clin Sci (Lond)*. 2008;114(3):243–249.

45. Ruttanaumpawan P, Gilman MP, Usui K, Floras JS, Bradley TD. Sustained effect of continuous positive airway pressure on baroreflex sensitivity in congestive heart failure patients with obstructive sleep apnea. *J Hypertens*. 2008;26(6):1163–1168.

46. Gupta N, Agrawal S, Goel AD, Ish P, Chakrabarti S, Suri JC. Profile of sleep disordered breathing in heart failure with preserved ejection fraction. *Monaldi Arch Chest Dis*. 2020;90(4):660–665.

47. Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19(12):1574–1585.

48. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J*. 2006;27(1):65–75.

49. Khan MS, Sreenivasan J, Lateef N, et al. Trends in 30- and 90-day readmission rates for heart failure. *Circ Heart Fail*. 2021;14(4):e008335.