Opiate Use and Escalation of Care in Hospitalized Adults with Acute heart failure and Sleep Disordered Breathing (OpiatesHF study)

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Running Head: Sleep disordered breathing, opiates and acute heart failure

This article has an online supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Abstract

Rationale: Sleep disordered breathing (SDB) is highly prevalent in adults hospitalized with acute heart failure. Data are limited on the implications of inadvertent opiate use in this population.

Objective: To determine the prevalence and impact of in-hospital opiate use in adults hospitalized for acute heart failure.

Methods: From a prospective sleep registry, we selected a sequential group of adult participants who were admitted to the hospital for acute heart failure and received a portable sleep study (PSS) after screening for SDB using the STOP-BANG questionnaire. A retrospective review of charts was performed to assess use of opiates, need for escalation of care (defined as transfer to the intensive care unit [ICU]), 30-day readmission and length of stay. A logistic regression model was used to calculate propensity scores for each participant with a screening apnea-hypopnea index (AHI) ≥ 10 /hour. Study endpoints, including escalation of care to the ICU and 30-day hospital readmission, were compared using a χ^2 test with stabilized inverse probability weighted propensity scores to control for potential confounding variables.

Results: A total of 301 consecutive adults admitted with acute heart failure between November 2016 through October 2017 underwent PSS after SDB screening. Overall, 125/301 (41.5%) received opiates in the hospital and 149 (49.5%) patients had an AHI ≥ 10 /hour by PSS (high risk of SDB). In this high-risk group, 47/149 (32%) received opiates. Among those with an AHI ≥ 10 /hour, escalation of care occurred in 12/47 (26%) of those who received opiates vs. 4/102 (4 %) of those who did not ($p < 0.001$, weighted estimate of treatment difference: 23.5%, 95% CI: 9.9, 37.2). Similarly, readmission within 30 days occurred in 7/47 (15%) of those who received opiates vs. 9/102 (9%) of those who did not ($p = 0.14$, weighted estimate of treatment

difference: 8.3%, 95% CI: -4.0, 20.6). Mean length of stay (days) did not differ between groups (p=0.61, weighted estimate of treatment difference: -0.3 days, 95% CI: -1.4, 0.8).

Conclusion: In adults admitted with acute heart failure and found to be at high risk of SDB, opiate use in the hospital was highly prevalent and was associated with a greater likelihood of escalation of care.

Sleep disordered breathing (SDB) is a highly prevalent disorder that is associated with significant cardiovascular mortality and morbidity (1,2,3,4). Recent data suggest that there is a high prevalence of SDB in patients admitted to the hospital with acute heart failure (5,6,7). Early detection and treatment intervention in hospitalized SDB patients with heart failure can reduce readmission (8,9).

Congestive heart failure is one of the most common causes of hospital admission in US; high readmission rates are noted as well (10,11,12,13). Historically, opiates, in particular morphine, have been used in the acute treatment of heart failure to reduce anxiety, dyspnea and produce vasodilation (14). However, its putative benefits have been called into question (14); in a large outcome study, morphine in the setting of acute heart failure was found to increase complications and mortality (15). In contrast, a recent retrospective study of congestive heart failure patients using opiates either on admission or at discharge did not find an increased readmission rate or mortality risk (16).

Opiates have been shown to worsen apneic events and lead to a precipitous drop in oxygenation due to suppression of medullary reflex ventilatory drive during sleep (17,18,19). Opiates also have been shown to induce or worsen central sleep apnea (20). Given these negative physiologic consequences of opiates, it is possible that their use in conjunction with undiagnosed SDB may be a factor contributing to adverse events in patients hospitalized with acute heart failure (21,22).

We hypothesized that administration of opiates in patients admitted for acute heart failure with undetected SDB may adversely impact patient outcomes during hospitalization. To address this issue, we studied the prevalence of opiate use in patients admitted with acute

heart failure who were identified as having SDB (apnea hypopnea index [AHI] ≥ 10 by portable sleep study [PSS]) to determine whether opiate use adversely impacted escalation of care (transfer to intensive care unit [ICU]), 30-day readmission rates and length of stay.

Methodology

This study was performed in an inner city safety net hospital with a predominantly African-American clientele with low socio-economic status. The study was approved by the Albert Einstein Medical Center Institutional Review Board. Informed consent was not required inasmuch as this was part of a hospital approved clinical pathway. A total of 1511 consecutive adult participants admitted to the cardiology telemetry services at Einstein Medical Center, Philadelphia, PA with a history of congestive heart failure were screened for SDB using the STOP-BANG questionnaire from November 2016 through October 2017 as part of our standard of care clinical practice guidelines. The STOP-BANG consists of Yes/No responses to 8 questions assessing whether the respondent snores [S], is tired, fatigued or sleepy [T], has been observed to be apneic during sleep [O], has an elevated blood pressure [P], has a body mass index (BMI) $> 35 \text{ kg/m}^2$ [B], is > 50 years of age or older [A], has a neck collar size [N] > 40 cm for females/ > 42 cm for males, and is of male gender [G]. An intermediate to high risk of SDB is a score ≥ 3 . The questionnaires were administered by a respiratory therapist. The admitting team was notified if the STOP-BANG questionnaire was positive (answering yes to 3 or more questions) who then consulted the pulmonary service for further evaluation of SDB and potential administration of a PSS.

As shown in online supplement Figure 1s, of 1511 adults screened with a STOP-BANG questionnaire during the period of this study, 712 had an intermediate to high risk of SDB and 301 patients received a PSS (Apnea Link Air TM, ResMed, San Diego, CA). The PSS procedure and a description of the Apnea Link Air are provided in the online supplement. The scoring of the PSS was performed by the device's automatic algorithm. However, the data were reviewed by a board-certified sleep physician.

The remaining screened cohort were excluded for the following reasons: high FiO₂ requirement (needing more than 2 lpm via nasal cannula), prior history of SDB (obstructive sleep apnea, obesity hypoventilation syndrome [OHS]) and on active therapy, admitted to the ICU directly from the emergency department and inability to follow commands or answer questions. The PSS was not necessarily performed on the night the opioids were administered.

The data were prospectively collected as part of a sleep registry at our institution and the hospital electronic medical record was reviewed to determine if the participants received opiates during that hospital stay but before transfer to the ICU. Participants were considered exposed to opiates if they received at least one dose during their stay in the hospital. Opiates were generally administered after the PSS, but the exact timing was not recorded. Participants who did not receive any dose of opiates (even if it was ordered) were placed in the non-opiates group. SDB was defined as an AHI ≥ 10 events per hour on PSS with a requirement that all hypopneas were associated with an oxygen desaturation drop of 4% or more. Patients were considered to have predominantly obstructive apnea if 50% or more of the events were obstructive in nature.

Subsequently, the cohort was subdivided into groups based on severity of AHI: No SDB (AHI <10 /hour), Mild ($10 \leq \text{AHI} < 15$ /hour), Moderate ($15 \leq \text{AHI} < 30$ /hour) and Severe (AHI ≥ 30 /hour)(23). Data pertaining to patient demographics, severity of SDB based on PSS, hospital length of stay, 30-day readmission and need for escalation of care during the hospital stay as defined by transfer to the ICU were obtained by medical record review. Participants' data were collected for up to 30 days following hospital discharge.

Statistical Analysis

All data were imported into SAS Version 9.4 software for statistical analysis. Descriptive statistics were generated for all baseline characteristics, sleep evaluations, and study endpoints including sample size, mean, standard deviation, and median for continuous parameters, and frequencies and percentages for categorical parameters.

A propensity score, the probability of being prescribed opiates, was calculated using logistic regression with age, race, BMI, cardiac ejection fraction, screening AHI category, STOP-BANG risk category, and key aspects of the medical history (hypertension, coronary artery disease, obstructive lung disease, history of pulmonary hypertension, diuretic use and anti-platelet use) to minimize the risks of potential bias inherent in non-randomized studies. Baseline variables were used as independent variables in a logistic regression model with an indicator variable that indicated whether the participant received opiates or not as the dependent variable. The propensity model was used to calculate propensity scores for each participant with a screening AHI ≥ 10 /hour, thus estimating the likelihood of each participant receiving opiates. Participants with AHI <10 were not included in the propensity model. Study

endpoints, including escalation of care to ICU and 30-day hospital readmission, were compared using a χ^2 test with stabilized inverse probability weighted propensity scores to control for potential confounding variables.

Comparison of mean length of stay in the hospital was performed with an analysis of variance using stabilized inverse probability weighted propensity scores to control for potential confounding variables. An additional analysis was performed for patients with a screening AHI <10 /hour comparing escalation of care to the ICU between treatment groups using an unweighted χ^2 test.

Results

A total of 301 adult participants admitted for acute heart failure received a PSS, of which 149 (49.5%) were identified as having SDB (screening AHI ≥ 10 /hour) and 125 (41.5%) received opiates in the hospital. Demographic and clinical information for the cohort found to have SDB are stratified by opiate usage and shown in Table 1. Those who were not administered any opiates during their hospitalization were slightly older (62.9 ± 13.0 vs. 59.5 ± 11.0 years), but the groups were otherwise similar in baseline characteristics. Fifty-four percent of participants with SDB were observed to have predominantly central apnea/ Cheyne-Stokes breathing, and 46% predominantly obstructive apnea. A summary of sleep test results (Table 1) did not show any significant differences in severity of sleep apnea or oxygen desaturation in comparisons of the opiate to the non-opiate group.

Table 2 describes the number of participants with SDB who required escalation of care stratified by opiate use; stratification by SDB categories is displayed in Figure 1. All events requiring escalation of care were due to acute respiratory failure/distress secondary to either hypoxia or hypercapnia. The percentage escalation was significantly greater in the SDB group receiving opiates compared to those who did not receive opiates (25.5% vs 3.9%, $p<0.001$, weighted estimate of treatment difference: 23.5%, 95% CI: 9.9, 37.2). Participants who did not have SDB but did receive opiates had a trend towards a higher rate of care escalation in comparison to those not administered opiates (14.1% vs 5.4%, $p=0.07$).

In participants with SDB, readmission within 30 days of the index hospitalization occurred at a higher rate in the group receiving opiates than in the group not receiving them although the difference was not statistically significant (14.9% vs 8.8%, $p=0.14$, weighted estimate of treatment difference: 8.3%, 95% CI: -4.0, 20.6). Length of stay (days) was not notably different between the two groups (mean 5.3 vs 5.5, $p=0.61$, weighted estimate of treatment difference: -0.3 days, 95% CI: -1.4, 0.8).

Discussion

This is the first study to our knowledge to assess the impact of opiate administration on escalation of care in patients with undiagnosed SDB admitted for acute heart failure. Thirty-two percent of these patients with SDB were administered opiates and were found to be at increased risk to have escalation of care as assessed by transfer to the ICU for acute respiratory failure or distress.

Sleep disordered breathing (SDB) is common in hospitalized patients (22). It is more prevalent in patients with heart failure (10,24) and is highly under diagnosed in cardiovascular patients in general. Consequently, many patients with SDB at the time of admission remain undiagnosed (25). The presence of SDB can increase the likelihood of CHF exacerbation and early intervention has been shown to reduce readmission rates and improve heart failure control (9,26). Furthermore, opiates are known to worsen SDB by increasing the number of events and aggravating associated oxygen desaturation (17-20,27-39). A recent study showed that opiate administration in the ICU increases risk of sleep apnea post-extubation (40). The same study revealed that a large proportion of the apneas post opioid administration in the ICU were obstructive as we found in our non-ICU cohort. Oxygen saturation has also been shown to drop precipitously—with a single dose of an opiate during sleep (20).

Opiates, benzodiazepines, barbiturates, and ethanol individually and additively suppress medullary reflex ventilatory drive during sleep especially during non-rapid-eye-movement sleep (30, 31). Therefore, death resulting from opiate ingestion is more likely to occur during sleep. Opiates also increase the number of SDB events in a dose related fashion (35). Increased SDB events may be related to adverse outcomes. Early diagnosis and intervention of SDB in the hospital may these reduce adverse outcomes (41,42).

This study reveals that use of opiates in patients admitted to the hospital for acute heart failure was as high as 41.5%. Use of opiates in the population having undiagnosed SDB (AHI ≥ 10) was also high (32%) and was associated with increased risk of escalation of care. Although opiates alone increased the likelihood of ICU transfer, the need for escalation of care appeared to be higher when opiates were administered in those with concomitant SDB. While there was

a trend towards increased 30-day readmission in patients administered opiates, there was no statistical difference. This finding occurred despite complex interactions among heart failure, cardiac arrhythmias and sleep disordered breathing. In particular, central sleep apnea and Cheyne-Stokes Breathing should have contributed to higher 30-day readmission rates (43,44). There was no difference in length of stay between the groups. However, it is possible that confounders such as social and placement issues which are inherent in an under-privileged inner-city hospital may have been present.

This study has some limitations. Analysis was retrospective and non-randomized. It is possible that these findings are unique to the underserved population at our medical center due to poor socio-economic status and the increased probability of chronic therapeutic opiate use and abuse. Thus, replication of these findings at a dissimilar institution is warranted. In addition, there may have been some misclassification of patients' SDB status. Polysomnography is the gold standard for detection of SDB, but due to higher cost and complex logistics (e.g., transfer to a sleep laboratory, scheduling), it is not usually feasible as an inpatient procedure (45). However, our novel use in a hospital population of the STOP-BANG questionnaire in conjunction with a PSS has been validated and found to be clinically informative (22,25,46). Furthermore, the interval between admission and the PSS could have influenced the assessment of SDB severity. Sleep during hospitalization also is fragmented during the night. This may have reduced the accuracy of our estimate of SDB severity resulting in greater chance of misclassification of a patient's SDB severity status. Collectively, we feel that these concerns were minor, and there was likely little misclassification of SDB status, and any that occurred was non-differential and would have biased the findings to the null. Lastly, the number of

patients within each SDB category was small, which may have precluded our ability to fully understand the effect of SDB category on escalation of care.

Despite these limitations, the study suggests that opiates must be used with caution in patients admitted to the hospital with heart failure, especially those who may have unrecognized SDB. It also does not support the long-standing practice of using morphine in acute heart failure, especially in the presence of SDB. Thus, it provides important data which may impact the care and outcome of these patients in hospitalized settings. Targeted education for the clinicians and nurses should reduce the incidence of care escalation in these patients.

Conclusion

Patients admitted with acute heart failure and undiagnosed SDB have a high prevalence of receiving opiates. The use of opiates is associated with higher likelihood of escalation of care (ICU transfer). These outcomes may be mitigated by pro-active screening for sleep disorders and judicious use of opiates in this high-risk population.

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Table 1. Baseline characteristics of patients with Sleep Disordered Breathing (SDB) (AHI $\geq$ 10) with and without opiates exposure

Parameter	Mean $\pm$ SD, Median / n (%)	
	No Opiates (n=102)	Opiates (n=47)
Age (years)	62.9 $\pm$ 13.0, 65	59.5 $\pm$ 11.0, 59
Body Mass Index (kg/m ²)	33.5 $\pm$ 10.7, 31	35.2 $\pm$ 10.3, 33
African American	85 (83.3)	39 (83.0)
White	10 (9.8)	2 (4.3)
Other	7 (6.9)	6 (12.8)
Ejection Fraction (%)	41.1 $\pm$ 17.1, 45	42.0 $\pm$ 17.4, 50
EF <45%	48 (47.1)	19 (40.4)
EF $\geq$ 45%	54 (52.9)	28 (59.6)
Arterial Hypertension	65 (63.7)	35 (74.5)
Atrial Fibrillation	14 (13.7)	8 (17.0)
Obstructive Lung Disease	21 (20.6)	10 (21.3)
History of Pulmonary Hypertension	13 (12.7)	9 (19.1)
Diabetes Mellitus	40 (39.2)	22 (46.8)
Hyperlipidemia	36 (35.3)	19 (40.4)
Implantable Cardioverter Defibrillator	16 (15.7)	10 (21.3)
Coronary Artery Disease	26 (25.5)	18 (38.3)
Beta Blockers	64 (62.7)	31 (66.0)
ACE Inhibitors	40 (39.2)	20 (42.6)
Anti-Platelets	61 (59.8)	27 (57.4)
Angiotensin Receptor Blockers	14 (13.7)	4 (8.5)
Diuretics	65 (63.7)	27 (57.4)
AHI	33.5 $\pm$ 18.9, 30	35.0 $\pm$ 18.5, 35
Oxygen Desaturation <88% (minutes)	103.8 $\pm$ 109.8, 67	104.0 $\pm$ 83.7, 84

EF: ejection fraction, AHI: apnea-hypopnea index

Table 2. Analysis of Escalation of Care, Readmission and Length of Stay Patients with ScreeningAHI ≥ 10

	No Opiates	Opiates	P-value
No. of subjects	102	47	
Escalation of care (transfer to ICU)			
No. events	4	12	
Crude event rate (% transferred)	3.9	25.5	
Adjusted event rate (% transferred)*	3.4	26.9	
Adjusted event rate difference (95% CI)*		23.5 (9.9 to 37.2)	<0.001
Adjusted relative risk (95% CI)*		7.9 (2.5 to 24.7)	
Readmission within 30 days			
No. events	9	7	
Crude event rate (% readmitted)	8.8	14.9	
Adjusted event rate (% readmitted)*	8.4	16.7	
Event rate difference (95% CI)*		8.3 (-4.0 to 20.6)	0.14
Adjusted relative risk (95% CI)*		2.0 (0.8 to 5.0)	
Length of stay (days)			
Mean $\pm$ SD	5.5 $\pm$ 2.9	5.3 $\pm$ 3.9	
Adjusted mean $\pm$ SD*	5.6 $\pm$ 2.9	5.3 $\pm$ 3.7	
Adjusted mean difference (95% CI)*		-0.3 (-1.4 to 0.8)	0.61

*Analysis performed using stabilized inverse probability weighted propensity scores to control for potential confounding variables

CI = confidence interval, SD = standard deviation

Figure Legend:

Figure 1. Escalation of care in patients with SDB (AHI $\geq$ 10) who received opioids compared to those who did not receive opioids: overall and according to AHI

Figure 1. Escalation of care in patients with SDB (AHI≥10) who received opioids compared to those who did not receive opioids: overall and according to AHI

Online Data Supplement

Opiate Use and Escalation of Care in Hospitalized Adults with Acute heart failure and Sleep Disordered Breathing (OpiatesHF study)

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Figure 1s (supp). Flowchart showing patient and group selection from inpatient sleep program

Portable sleep study equipment:

The ApneaLink Air (ResMed San Diego, Ca) is a market released portable device that has been FDA-cleared (K143272) where it may aid in the diagnosis of sleep disordered breathing for adult patients. The ApneaLink Air recorder is a 3-channel battery-powered respiratory pressure sensor and oximetry system. The default settings for the ApneaLink Air includes a flow reduction of 30% combined with a desaturation of 4%

Sleep disordered breathing, opiates and acute heart failure

to automatically score a hypopnea and a respiratory effort sensor to differentiate between central, obstructive and mixed apneas. The scoring was automatic and not manually scored. The data was reviewed by a Board-Certified Sleep Physician for study entry.

Method of portable sleep study in hospitalized adults:

The PSS was performed only at night. A trained respiratory therapist educated the patient and hooked up the device to the patient post dinner time (9-10 PM). The Nurses were familiarized with the device but were provided back pager number for the night RT who was available for trouble-shooting. A sign of sleep study was posted outside the door of the patient room to encourage minimal interruptions. The Device was unhooked between 6.30 – 7 AM by the night RT before his shift ended. Patient was quizzed by the RT on the quality of his sleep. A minimum of 2 hours of cannula recording time was required. If patient sleep quality was poor (patient reported minimal or no sleep) and /or cannula time found to be less than 2 hours the study was repeated the subsequent night.