Sleep Related Breathing Disorders and Neurally Mediated Syncope (SRBD and NMS)

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Abstract

Introduction: Individuals with severe sleep related breathing disorders (SRBD) tend to experience intermittent hypoxia, sleep fragmentation and highly fluctuating intrathoracic pressures. Chronic exposure to these stressors sensitizes the parasympathetic system while suppressing the sympathetic system. Parasympathetic over-reactivity among patients with severe sleep related breathing disorders has been proposed as a predisposing factor for neurally mediated syncope.
Goal: We sought to determine the relative risk for neurally mediated syncope in patients with severe SRBD compared to the general population.
Methods: This is a retrospective cohort study of 228 cases selected from 2,598 patients who were referred for polysomnography on discharge from hospitalization. Incidence of neurally mediated syncope (NMS) was compared between patients with apnea-hypopnea-index (AHI) scores of 30 or greater and those with an AHI score below 5.
Results: Approximately 32% of patients with severe SRBD had a history of neurally mediated syncope compared to only 14% in patients with normal sleep breathing patterns (OR = 3.09, 95% CI: 1.25 - 7.62, p = 0.015).
Conclusion: Our multi-center retrospective study supports an association between SRBD and NMS.

Brief Summary

Current Knowledge/Study Rational. There are multiple reports that highlight a possible connection between sleep related breathing disorders and neurally mediated syncope. Deleterious effects on the autonomic and peripheral nervous system by severe sleep related breathing disorders have also been demonstrated. We sought to determine the association and relative risk of neurally mediated syncope in patients with severe sleep related breathing disorders.

Study Impact. Patients with severe sleep related breathing disorders are at increased risk for neurally mediated syncope. Early identification and appropriate treatment in this patient population may reduce rates of syncope, improve quality of life and clinical outcomes.

Introduction

Sleep related breathing disorders (SRBD), comprise a spectrum of disorders characterized by chronic intermittent apnea and hypopnea, which includes obstructive sleep apnea (OSA), central sleep apnea, sleep-related hypoventilation, and nocturnal hypoxemia (1). Neurally mediated syncope (NMS), also known as reflex syncope, is defined as a transient loss of consciousness secondary to decreased cerebral blood supply, typically as a result of reflexive cardiac inhibition and decreased vascular tone. NMS includes vasovagal syncope, situational syncope and carotid sinus syncope (2). Autonomic dysfunction may also play a role in cases of NMS (3). Researchers have previously documented the deleterious effects of SRBD on the autonomic and peripheral nervous system (4-7). A connection between SRBD and NMS has been proposed by some, detailing cases of patients suffering from incapacitating recurrent syncope which demonstrates dramatic improvement or resolution after diagnosis and treatment of OSA (8-10). In this study, we sought to determine the association and relative risk of neurally mediated syncope in patients with severe sleep related breathing disorders.

Methods

This retrospective cohort analysis was performed using electronic medical record data collection from hospitals within the Kettering Health Network, including Fort Hamilton Hospital (Hamilton, Ohio), Grandview Medical Center (Dayton, Ohio), Greene Memorial Hospital (Xenia, Ohio), Kettering Medical Center (Kettering, Ohio), Soin Medical Center (Beavercreek, Ohio), Southview Medical Center (Centerville, Ohio) and Sycamore Medical Center (Miamisburg, Ohio). Individuals who underwent and completed in-facility polysomnography were selected for study review. Patients under the age of 18 years old and those with a pacemaker or implantable cardiac defibrillator were excluded from the study. Patients were divided into two groups; those with severe SRBD, defined as having an Apnea-Hypopnea Index (AHI) score of/ or greater than 30, and a control group, defined as patients having an AHI score of/ or less than 5. This study was approved by the institutional review board (IRB) at Kettering Health Network.

Statistical Methods: The Kolmogorov-Smirnov and Shapiro-Wilk tests were utilized to compare baseline patient demographics between each group; control and severe SRBD group. These tests were selected to better represent the data, with median interquartile range (IQR), as outliers were included in the analysis. Categorical variables were compared using Pearson's Chi-squared test. Continuous variables were compared using the Student's t-test or Wilcoxon rank sum test (Mann-Whitney U test). All estimates were reported as 95% confidence intervals with p-values. Two-sided p-values less than 0.05 were considered statistically significant. Multivariate logistic regression

modeling was used to determine the effects of each variable while controlling for confounding variables. Odds ratios (OR) were calculated for each type of syncope in both the severe SRBD group and control group. All statistical analyses were performed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 2,598 patients were identified from the electronic medical record database, of which, only 228 patients fulfilled our inclusion criteria for severe SRBD (AHI score of/ or greater than 30), with 80 patients meeting criteria for the control group (AHI score of/ or less than 5). Among the 228 patients with severe SRBD, the most common subtype was obstructive sleep apnea (204 of 228 patients, 89.5%), followed by central sleep apnea (13 of 228 patients, 4.2%) and mixed type (11 of 228 patients, 3.6%).

Initial comparison of demographic characteristics (Table 1) was done using univariate analysis.

Table 1: Baseline Characteristics of the Individuals with and without SRBD.

Variable	SRBD (N = 228)	Control (N = 80)	p value
Age (years), Median (IQR)	67.0 (58.0-75)	61.0 (58.0-72.5)	0.079
Male, N (%)	142/22 (62.3)	38/80 (47.5)	0.021
BMI (kg/m^2), Median (IQR)	36.5 (31.3-43.8)	34.4 (27.3-40.4)	0.042
AHI, Median (IQR)	53.2 (38.7-80.2)	1.6 (0-2.6)	<0.001
Sleep apnea type			
Obstructive sleep apnea, N (%)	204/228 (89.5)	N/A	N/A
Central sleep apnea, N (%)	13/228 (4.2)	N/A	N/A
Mixed sleep apnea, N (%)	11/228 (3.6)	N/A	N/A
Comorbidities			
Hypertension, N (%)	172/228 (75.4)	43/80 (53.8)	<0.001
Diabetes Mellitus Type I or II, N (%)	135/228 (59.2)	48/80 (60.0)	0.902
Coronary artery disease, N (%)	98/228 (43.0)	25/80 (31.3)	0.065
COPD, N (%)	68/228 (29.8)	35/80 (43.8)	0.023
LVEF <55%, N (%)	71/228 (31.1)	14/80 (17/5)	0.19
Pulmonary artery pressure, Median (IQR)	32.5 (24.9-39.8)	31.0 (17.1-38.2)	0.226

SRBD: sleep-related breathing disorder, IQR: interquartile range; BMI: body-mass index; AHI: apnea-hypopnea index; LEVF: left ventricular ejection fraction; COPD: chronic obstructive pulmonary disease; N: number; N/A: not applicable.

The SRBD group and control did not statistically significance differ in age (p = 0.79). Although gender differences were noted, 62.3% male in the SRBD group compared to 47.5% in the control group (p = 0.042), there were no statistically significant differences on multivariate logistic regression (p = 0.854). Differences in body mass index (BMI) between groups were noted on univariate (p = 0.042) and multivariate models (p = 0.041), with 36.5 (IQR 31.3 – 43.8) mean BMI of the SRBD group compared to 34.4 (IQR 27.3 – 40.4) in the control group.

The incidence of pre-existing comorbidities between groups was also compared. (Table 1) There were no statistically significant differences between the groups in terms of pulmonary artery pressure (p = 0.226), diabetes (p = 0.902) and coronary artery disease (p = 0.065). Univariate analysis did reveal differences amongst left ventricular ejection fraction (LVEF), 31.1% of patients with SRBD had LVEF <55% compared to only 17.5% in the control group (p = 0.19), hypertension (HTN), 75.4% of patients with SRBD had HTN compared to only 53.8% in the control group (p < 0.001), and chronic obstructive pulmonary disease (COPD), 29.8% of patients with SRBD compared to 43.8% in the control group (p = 0.023). These findings were not statistically significant on multivariate logistic regression; LVEF<55% (p = 0.326), HTN (p = 0.585), COPD (p = 0.576).

The mean apnea hypopnea index (AHI) for the severe SRBD group was 53.2 (38.7-80.2), compared to 1.6 (0-2.6) in the control group (p < 0.001). The prevalence of NMS was higher in the SRBD group compared to the control group, 32% (73 of 228 patients) and 14% (11 of 80 patients), respectively; χ^2 (2, N=308) = 9.96, p = 0.001. Prevalence of non-neurally mediated syncope did not differ significantly between the SRBD group and control group, 1% (2 of 228 patients) and 0% (no patients), respectively; Pearson's Chi-squared test p = 0.571. Approximately 32% of patients with severe SRBD had a history of neurally mediated syncope compared to only 14% in patients with normal sleep breathing patterns (OR = 3.09, 95% CI: 1.25 - 7.62, p = 0.015). (Table 2).

Table 2: Multivariate Logistic Regression Modeling, Odds Ratio (OR) for Neurally Mediated Syncope.

Variable	Odds Ratio (95% CI), p value
Male	1.05 (.616-1.80), p=0.854
BMI (kg/m^2)	1.03 (1.00-1.06), p=0.041
AHI	0.999 (.990-1.01), p=0.896
LEVF <55	1.37 (.743-2.51), p=0.316
Hypertension	0.848 (.468-1.53), p=0.585
COPD	0.850 (.481-1.50), p=0.576
Sleep-related breathing disorder	3.09 (1.25-7.62), p=0.015

CI: confidence interval; BMI: body mass index; AHI: apnea-hypopnea index; LEVF: left ventricular ejection fraction; COPD: chronic obstructive pulmonary disease.

Situational syncope has not been consistently recorded, OR and CI were not calculated.

Discussion

This study suggests that individuals with severe sleep related breathing disorders are at increased risk for developing neurally mediated syncope. Chrysostomakis *et al.* (11) showed that parasympathetic activity is increased during the night in patients with obstructive sleep apnea and that continuous positive airway pressure (CPAP) treatment may restore autonomic balance. Puel *et al.* (8) suggested that intermittent hypoxia, sleep fragmentation and variations of intra-thoracic pressures may result in chronic

adaptations to the autonomic nervous system, which may predispose patients to vasovagal syncope. Cintra *et al*. (12) noted that patients with vasovagal syncope exhibited sympathetic suppression during rapid eye movement (REM) sleep. Previous studies indicate that chronic intermittent hypoxia can also increase activation of free-radical oxidation, which in turn can elicit rapid and sustained expression of pro-inflammatory cytokines (12). This oxidative stress and inflammatory response can induce tissue damage and intermittent academia, eventually leading to up-regulation of pH sensitive ion channels on chemo-afferent neurons at the carotid bodies. Overexpression of these channels potentiates the carotid body response to changes in arterial oxygen saturation (12). It is possible that this mechanism also contributes to the higher prevalence of carotid sinus hypersensitivity and syncope among patients with severe SRBD. In accordance with our findings, there have been reported cases of recurrent syncope, which have resolved with correction of underlying SRBD (8-10). Appropriate management of SRBD in this patient population may reduce rates of NMS. Given the high prevalence of SRBD and neurally mediated syncope in the United States, further investigation is warranted to delineate the association between the two disease processes and the mechanisms which are involved.

Study Limitations

Our retrospective study design has limited control over consistency and accuracy. This study did not use any matching algorithm to match the control group to the individuals with severe SRBD for baseline characteristics. We did not utilize a caliper matching process to identify controls, and as a result, the control cohort was smaller than the study cohort. The diagnosis of vasovagal syncope was made based on clinical presentation. All patients who were diagnosed with vasovagal syncope did not have confirmatory tilt-table testing, limiting diagnostic accuracy and consistency.

Conclusion

Our study suggests that individuals with severe sleep-related breathing disorders (SRBD) are approximately 3 times (OR = 3.09, 95% CI: 1.25 - 7.62, p = 0.015) more likely to have experienced neurally mediated syncope (NMS) compared to case matched controls.

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