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# Sex-Stratified Analysis of Airway Collapsibility Among Individuals Undergoing Chronic Opioid Therapy

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*Abstract*— **Opioids, known for suppressing respiration and reducing upper airway dilator muscle activity, contribute to increased risk of airway collapsibility and obstructive sleep apnea (OSA). This study addresses the existing gap in understanding the sex-specific impact of opioids therapy on airway dynamics during sleep, investigating differences in airway collapsibility among sexes. To address this goal, sleep studies of 44 participants on chronic opioids therapy who had OSA were analyzed. Airway collapsibility was estimated based on the ratio of obstructive apneas and hypopneas. Our results showed that while the severity of OSA was significantly higher in men than women during total sleep time and non-rapid eye movement sleep stage, the airway collapsibility was not statistically different. Moreover, we observed that there is an interaction effect between body mass index and sex as well as opioids dosage in modeling the airway collapsibility.**

*Keywords*— **Opioids, Obstructive Sleep Apnea, Airway Collapsibility, Modeling.**

## I. Introduction

Opioids, the mainstream therapy for moderate-to-severe chronic pain, decrease respiratory drive and activity of upper airway dilator muscles [1], leading to increased airway collapsibility, a key contributor to obstructive sleep apnea (OSA).

OSA is characterized by recurrent episodes of complete (apnea) or partial (hypopnea) airway obstruction during sleep. The severity of OSA is assessed based on the number of apneas and hypopneas per hour of sleep, known as apnea-hypopnea index (AHI). Sleep apnea has been associated with a myriad of adverse acute and chronic cardiovascular complications such as respiratory depression, pulmonary hypertension, stroke, coronary artery disease, and heart failure [2-5].

OSA is highly prevalent in the general population [6, 7] and in individuals on chronic opioids therapy [1, 8], with its rate ratio demonstrating dose dependency [9]. Compared to women, the prevalence of OSA is higher in men both in general population [6] and in individuals on chronic opioids therapy [1]. The overall prevalence of sleep apnea (AHI≥5 with symptoms of daytime sleepiness) in general population is estimated at 14% for men and 5% for women, with moderate-to-severe sleep apnea (AHI≥15) affecting men more than 2 times than women [6, 10]. In individuals on chronic opioids therapy, the prevalence of OSA is between 14 to 36% [11] with moderate-to-severe OSA affecting 55% of men [1].

Despite the well-established concern surrounding the opioids induced OSA, there exists a significant gap in our understanding regarding sex-based differences in how opioids therapy may influence airway dynamics during sleep. This is crucial for developing sex-specific OSA management and opioid use guidelines to improve patient outcomes and reduce cardiovascular risks associated with OSA. Thus, in this study we investigated the differences of airway collapsibility due to opioids among sexes.

## II. Methods and Materials

To address the objective of this project, we retrospectively analyzed the sleep study of 44 participants (18+ years old, 24 women), who were on chronic opioids therapy for >3 months with a stable daily dose >4 weeks to manage non-cancerous pain. Inclusion criteria was 1) presence of OSA (AHI≥5 in which ≥50% of events were obstructive) and 2) availability of the information regarding number of obstructive apneas and hypopneas.

Sleep studies were performed at University Health Network (Toronto) or the London Health Sciences (London, Canada) laboratories using polysomnography recordings. Sleep studies were scored according to the guideline of American Academy of Sleep Medicine (2012) [12]. Apnea

was characterized by at least 90% reduction in airflow signal lasting at least 10 seconds. Hypopnea was characterized as an episode lasting at least 10 seconds in which airflow signal or sum of chest and abdomen signals were reduced by at least 30% and it was accompanied by a desaturation of at least 3% in oxygen and/or an arousal from sleep. Apneas and hypopneas were classified as obstructive if respiratory efforts were present. Obstructive AHI was determined as the hourly average frequency of obstructive apneas and hypopneas. Airway collapsibility was calculated as the ratio between obstructive apneas and hypopneas, a surrogate of Pcrit [7].

The variables describing participants' demographics, sleep apnea, and airway collapsibility were compared between and within sexes using t-test or Wilcoxon two sample test, based on the normality distribution of the data. To gain a better understanding of the effect of age, body mass index (BMI), and opioids dosage on sex differences of airway collapsibility, we systematically categorized patients and examined the variations in airway collapsibility between and within each group. Stratification process was performed based on the histogram of the variables to ensure an equitable distribution of data in each group, aiming for similarity in the number of data points across the groups. Age and BMI was stratified using the cutoff of 55 years old, and 30 $kg/m^2$, respectively. Opioids dosages for each participant were converted to milligram morphine equivalent (MME) based on the guidelines provided by the US Centers for Disease Control and Prevention [13] and were categorized using the cutoff of 50 MME.

To better understand the dynamics of airway collapsibility during sleep, we also investigated the differences of airway collapsibility in non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stages. To study the impact of the interaction among variables, we formulated a model for airway collapsibility, taking into account participants' sex, BMI, and opioid dosages. Age was omitted from this model as there was no statistically significant difference in airway collapsibility across different age categories. It is important to note that we did not employ stratified variables for this particular analysis. A p-value of <0.05 was considered statistically significant. A p-value of 0.05-0.1 were considered borderline significant. All statistical analysis were performed in JMP Pro 17.

## III. Results

The demographics of participants are presented in Table 1. There were similar number of men (45.45%) and women (54.55%) with OSA in the data. In this population, the prevalence of moderate-to-severe OSA was higher in men than women (67% vs. 33%). The age, BMI, and opioids dosage were not significantly different between men and women ($p > 0.05$ for all).

Total AHI and obstructive AHI was significantly higher in men than women (total AHI: 26.16 ± 18.50 vs. 14.00 ± 12.97, $p = 0.002$, obstructive AHI: 24.02 ± 18.44 vs. 12.87 ± 12.50, $p = 0.003$). In both men and women, the events were predominantly hypopneas rather than apneas during total sleep time, NREM and REM sleep stages ($p < 0.0001$ for all). Compared to women, men had significantly elevated number of obstructive hypopneas during total sleep time (103.70 ± 80.45 vs. 54.39 ± 47.18, $p = 0.018$) and NREM sleep stage (79.27 ± 70.15 vs. 34.81 ± 42.97, $p = 0.016$). The difference was not significant in REM sleep stage ($p = 0.942$). Moreover, there were no significant differences on obstructive apneas and airway collapsibility between men and women during total sleep time, NREM, and REM sleep stages ($p > 0.05$ for all).

Table 1 Participants Demographics

| | Total | Women | Men | p |
|---|---|---|---|---|
| **N (%)** | 44 (100.0) | 24 (54.55) | 20 (45.45) | 0.546 |
| **Age** | 55.55 ± 11.21 | 56.62 ± 8.84 | 54.25 ± 13.40 | 0.496 |
| **BMI** | 30.45 ± 6.24 | 31.55 ± 6.88 | 29.12 ± 5.07 | 0.208 |
| **Opioids** | 89.44 ± 103.17 | 81.35 ± 86.81 | 99.15 ± 119.16 | 0.813 |
| **AHI** | 19.53 ± 16.86 | 14.00 ± 12.97 | 26.16 ± 18.50 | **0.002** |
| **OAHI** | 17.94 ± 16.45 | 12.87 ± 12.50 | 24.02 ± 18.44 | **0.003** |
| **AHI≥15** | 18 (100.0) | 6 (33.33) | 12 (66.67) | 0.153 |
| **Obstructive Apnea** | | | | |
| **TST** | 10.25 ± 24.24 | 10.46 ± 25.24 | 10.00 ± 22.97 | 0.782 |
| **NREM** | 7.40 ± 19.11 | 7.35 ± 18.46 | 7.47 ± 19.94 | 0.505 |
| **REM** | 3.68 ± 8.21 | 4.33 ± 9.72 | 2.90 ± 5.83 | 0.532 |
| **Obstructive Hypopnea** | | | | |
| **TST** | 77.33 ± 69.32 | 54.39 ± 47.18 | 103.70 ± 80.45 | **0.018** |
| **NREM** | 53.33 ± 60.07 | 34.81 ± 42.97 | 79.27 ± 70.15 | **0.016** |
| **REM** | 22.16 ± 15.18 | 22.00 ± 14.68 | 22.35 ± 15.74 | 0.942 |
| **Airway Collapsibility** | | | | |
| **TST** | 0.13 ± 0.23 | 0.16 ± 0.28 | 0.08 ± 0.15 | 0.202 |
| **NREM** | 0.09 ± 0.18 | 0.12 ± 0.21 | 0.06 ± 0.14 | 0.152 |
| **REM** | 0.14 ± 0.33 | 0.17 ± 0.40 | 0.10 ± 0.22 | 0.333 |

N: Number, MME: Milligram Morphine Equivalent, AHI: Apnea-Hypopnea Index, OAHI: Obstructive AHI, TST: Total Sleep Time, (N)REM: (Non-) Rapid Eye Movement, p: p-value

Units: Age -> years, BMI -> $kg/m^2$, Opioids -> MME/d, (O)AHI -> $hr^{-1}$, AHI≥15 -> N(%), Obstructive Apnea(Hypopnea) -> N

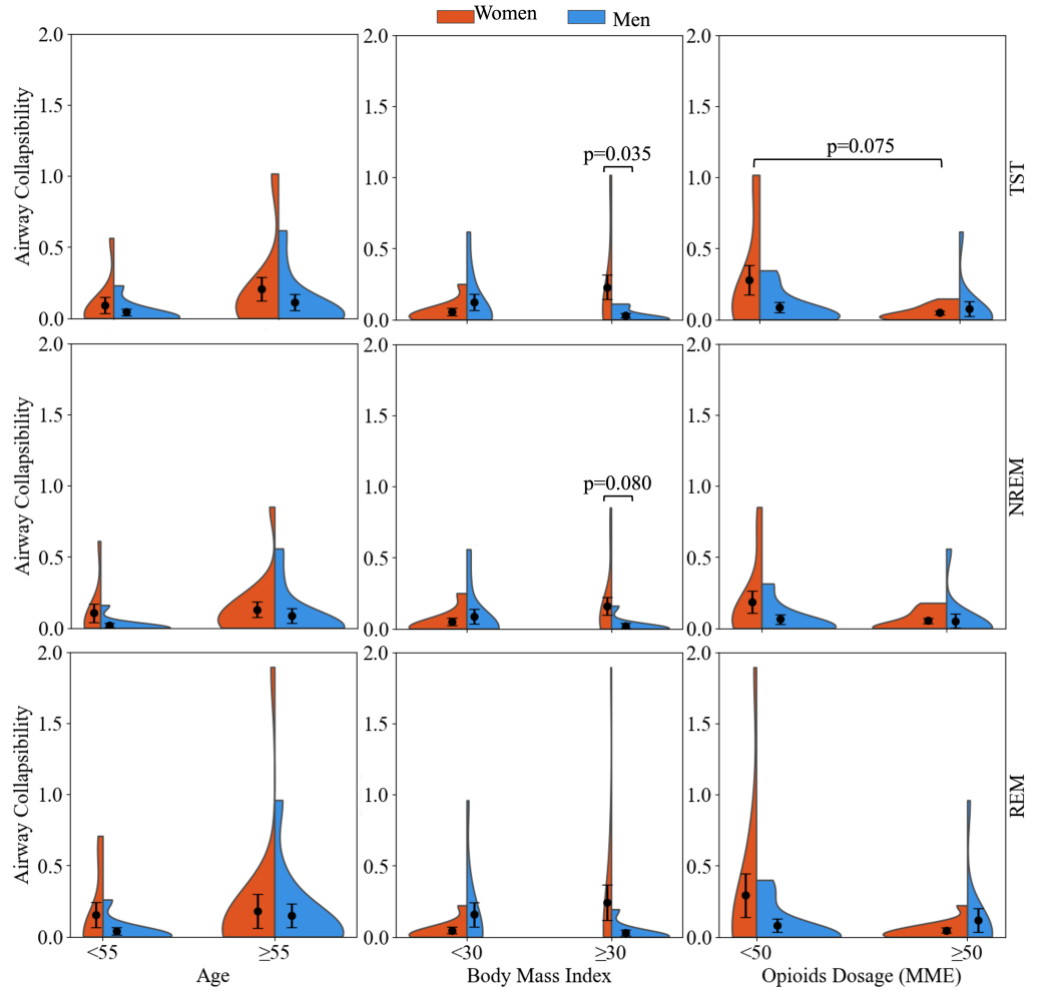


Fig. 1 Airway Collapsibility in Relation to Age (left), BMI (middle), and Opioids Dosages (right) during Total Sleep Time (up), Non-Rapid Eye Movement (middle), and Rapid Eye Movement (down) Sleep Stages. p: p-value

Compared to men with BMI≥30 kg/m$^2$, women had significantly higher airway collapsibility during sleep time (0.23 ± 0.35 vs. 0.03 ± 0.04, p = 0.035) and borderline higher airway collapsibility during NREM sleep (0.16 ± 0.25 vs. 0.02 ± 0.05, p = 0.080). The airway collapsibility was borderline higher in women on opioids dosage <50 MME compared to those on opioids dosage ≥50 MME (0.28 ± 0.37 vs. 0.05 ± 0.05, p = 0.075). The airway collapsibility model revealed that the interaction terms of Sex:BMI and Opioids:BMI significantly contributed to the variability in airway collapsibility during total sleep time, NREM, and REM sleep stages.

Table 2 Airway Collapsibility Model

| **Airway Collapsibility** | **TST** | **NREM** | **REM** |
|---|---|---|---|
| **Model RSquare** | 0.37 | 0.39 | 0.40 |
| **Model p-value** | **0.006** | **0.005** | **0.003** |
| **Variables p-value** | | | |
| **Sex** | 0.302 | 0.224 | 0.589 |
| **BMI (kg/m$^2$)** | 0.637 | 0.702 | 0.729 |
| **Opioids (MME/d)** | 0.701 | 0.682 | 0.948 |
| **Sex : BMI** | **0.012** | **0.012** | **0.010** |
| **Sex : Opioids** | 0.169 | 0.595 | 0.127 |
| **Opioids : BMI** | **0.048** | **0.027** | **0.014** |

BMI: Body Mass Index, MME: Milligram Morphine Equivalent

## IV. Conclusion

In this project, we studied the sex-based differences of opioids' impact on airway collapsibility during sleep. Our results showed that while men had significantly higher AHI and obstructive AHI than women during total sleep time and NREM sleep stage, the airway collapsibility was not significantly different. These results suggest that the increased AHI in men is possibly due to the increased hypopnea events due to opioids rather than elevated airway collapsibility. Our results revealed an interaction effect between sex and BMI as well as opioids and BMI in modeling the airway collapsibility.

In both men and women on chronic opioids therapy, we observed that airway collapsibility was lower than the previously published values for general population during total sleep time, NREM and REM sleep stages [7]. This finding is likely attributed to the significant increase in obstructive hypopneas due to opioids. Moreover, we found out that in individuals on chronic opioids therapy, the average airway collapsibility was not significantly different between men and women during total sleep time and NREM sleep stage, contrary to the general population where women have lower airway collapsibility than men [7]. In REM sleep, airway collapsibility was similar between men and women on chronic opioids therapy, consistent with the general population [7].

While this study is limited by the sample size and associated statistical power, it provides valuable insights into the changes in airway collapsibility among sexes in individuals on chronic opioids therapy. Future studies, with larger sample sizes and enhanced statistical power, are required to comprehensively elucidate the dynamics of airway collapsibility, its determinants, and their interactions among sexes. This will significantly contribute to a more nuanced understanding of the complex interplay between sex, chronic opioids therapy, and airway dynamics and potential therapeutic options to reduce the adverse outcomes of opioids induced sleep apnea.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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