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ORIGINAL RESEARCH

Hyperinflation is Associated with Lower Sleep Efficiency in COPD with Co-existent Obstructive Sleep Apnea

Jeff S. Kwon, MD[1] (jkw109@gmail.com), **Lisa F. Wolfe, MD**[2] (lwolfe@northwestern.edu), **Brandon S. Lu, MD, MS**[1] (brandon-lu@md.northwestern.edu), and **Ravi Kalhan, MD, MS**[2] (r-kalhan@northwestern.edu)

[1]*Department of Neurology, Center for Sleep and Circadian Biology, Northwestern University Feinberg School of Medicine, Chicago, IL*
[2]*Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, 240 E. Huron St. McGaw M300, Chicago, IL*

ABSTRACT

Prior research has shown that individuals with obstructive lung disease are at risk for sleep fragmentation and poor sleep quality. We postulated that patients with chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (known as overlap syndrome) who have more severe lung disease, as measured by lung hyperinflation (inspiratory capacity/total lung capacity), would have greater sleep disturbances independent of traditional measures of sleep apnea. We performed a retrospective chart review of consecutive patients evaluated and treated in an academic pulmonary clinic for overlap syndrome. Pulmonary function tests and polysomnogram data were collected. Thirty patients with overlap syndrome were included in the analysis. We found significant univariable associations between sleep efficiency and apnea/hypopnea index ($\beta = -0.285$, $p = 0.01$) and between sleep efficiency and lung hyperinflation ($\beta = 0.654$, $p = 0.03$). Using multivariable linear regression, the relationship between sleep efficiency and lung hyperinflation remained significant ($\beta = 1.13$, $p = 0.02$) after adjusting for age, sex, body mass index, apnea/hypopnea index, FEV_1% predicted, oxygen saturation nadir, medications, and cardiac disease. We conclude that increased severity of hyperinflation is associated with worse sleep efficiency, independent of apnea and nocturnal hypoxemia. The mechanisms underlying this observation are uncertain. We speculate that therapies aimed at reducing lung hyperinflation may improve sleep quality in patients with overlap syndrome.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), known as "overlap syndrome", experience pronounced nocturnal hypoxemia, sleep fragmentation and reduced quality of life (1–3). It has been our experience that many patients with COPD and OSA continue to subjectively experience poor quality sleep and daytime fatigue, despite receiving therapies to alleviate apnea events and nocturnal hypoxemia. This implies other pathophysiologic mechanisms play a role in sleep disturbance and insomnia reported by patients with obstructive lung disease and OSA (4–10).

Prior reports indicate that severity of lung disease based on forced expiratory volume in 1 second (FEV_1) is not associated with changes in sleep quality in patients with obstructive lung disease (11). However, FEV1 has been shown to correlate poorly with other patient-centered outcomes, such as exercise capacity and dyspnea (12). In contrast, lung hyperinflation, which is the ratio of inspiratory capacity to total lung capacity (IC/TLC), has been proposed as a superior measure of lung disease severity over FEV_1 in patients with COPD due to its ability to better predict mortality (13). To our knowledge, the impact of lung hyperinflation on objective sleep quality has not been studied.

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Correspondence to:
Jeff S. Kwon, MD
Asthma-COPD Program
Division of Pulmonary and Critical Care Medicine and Department of Neurology
Northwestern University Feinberg School of Medicine
Chicago, IL 60611
phone: (312) 503-1539; fax: (312) 503-5679
email: jkw109@gmail.com

We postulated that patients with more severe lung hyperinflation would have increased sleep disruption independent of traditional measures of sleep apnea in patients with overlap syndrome, and that IC/TLC would be more strongly associated with changes in sleep architecture over FEV_1.

METHODS

This investigation was a retrospective chart review of consecutive patients evaluated and treated in an academic tertiary care pulmonary clinic for chronic obstructive pulmonary disease between January 2004 and August 2007. Eligible subjects were identified by searching the pulmonary clinic discharge ICD-9 code 496 diagnosis of COPD and the presence of a diagnostic polysomnogram order in the chart. A diagnosis of COPD documented in the chart by a pulmonary specialist, and the presence of obstructive sleep apnea (Apnea/Hypopnea Index > 5) confirmed by an attended overnight diagnostic polysomnogram were required for inclusion in this analysis.

Only subjects who had a pulmonary function test and a polysomnogram (Nihon Kohden) performed within 2 years were included in the analysis. COPD patients referred to the sleep laboratory without full pulmonary function tests within 2 years were excluded. Subjects were also excluded from the analysis if there was a known or clinically suspect diagnosis of pulmonary disease other than COPD, including asthma and interstitial lung disease. In addition, subjects were excluded from the analysis if there was a known or clinically suspect diagnosis of a primary sleep disorder other than OSA, including narcolepsy, idiopathic hypersomnia, primary insomnia, or restless legs syndrome.

Pulmonary function data included spirometry and lung volumes. RV/TLC (residual volume/total lung capacity) and IC/TLC (inspiratory capacity/total lung capacity $\times$ 100) ratios were recorded as measures of air trapping and lung hyperinflation respectively. The data collected from polysomnograms included apnea/hypopnea index (AHI), arousal index, overnight oxygen saturation nadir (SpO_2 nadir), % time of overnight oxygen saturation less than 90% (T90), sleep efficiency (total sleep time/total recording time), sleep latency, and total sleep time.

Medication lists were also reviewed from the chart and use of tiotropium, long-acting beta agonists (LABA), inhaled corticosteroids (ICS), oral steroids, and theophylline were recorded. Co-morbid cardiac disease was defined as having a documented history of coronary artery disease, congestive heart failure, or atrial fibrillation/flutter. Essential hypertension was not included as a co-morbid cardiac condition. All pulmonary function tests and polysomnograms were performed at the pulmonary function and sleep labs at Northwestern Memorial Hospital, Chicago. The sleep lab is a 14-bed accredited lab that serves as the primary diagnostic center for sleep disorders for a tertiary academic medical center and the surrounding Chicago area. Approximately 2500–2700 studies are performed at this laboratory per year, and approximately 90% of patients are diagnosed with obstructive sleep apnea.

Table 1. Data represents mean $\pm$ SD

Characteristics	Mean value $\pm$ SD
Age, yr	65.9 $\pm$ 1.8
BMI, kg/m^2	34.2 $\pm$ 1.08
FEV1 % predicted	57.0 $\pm$ 3.28
FVC % predicted	63.6 $\pm$ 2.58
FEV1/FVC	64.1 $\pm$ 2.61
IC/TLC	34.5 $\pm$ 1.79
RV/TLC	51.9 $\pm$ 1.82
AHI	21.8 $\pm$ 4.81
Sleep Efficiency	72.5 $\pm$ 3.0
Total Sleep Time, min	291.2 $\pm$ 15.87
Sleep Latency, min	23.8 $\pm$ 5.46
Arousal index	24.9 $\pm$ 3.26
Epworth Sleepiness Score	8.6 $\pm$ 0.96

*BMI = body mass index; FEV1 = forced expiratory volume in 1 second; FVC = forced volume capacity; IC = inspiratory capacity; TLC = total lung capacity; RV = reserve volume; AHI = apnea/hypopnea index.

Statistical analysis

The relationships between a given continuous variable of interest and sleep efficiency and sleep latency were assessed with simple correlation. For all independent variables included in the analysis, density plots were made to visually assess their distribution. Each variable appeared normal distributed. Multivariable linear regression was employed to evaluate the relationship between lung function and sleep parameters independent of sleep apnea. Co-variables included in the statistical models were pre-specified based on a known or hypothesized association with sleep efficiency in the overlap syndrome (14–17). All analyses were performed using STATA 9.2 (STATA Corp, College Station, TX).

RESULTS

Thirty patients were included in the study. Demographic characteristics are included in Table 1. There were 18 males and 12 females. Subjects had a mean age and mean BMI of 65.9 $\pm$ 1.81 years and 34.26 $\pm$ 1.08 kg/m^2, respectively. The severity of OSA was generally moderate with a mean AHI of 21.80 $\pm$ 4.81. Mean sleep efficiency was 72.5% $\pm$ 3.01. Mean FEV_1 % predicted was 57.03 $\pm$ 3.28 and mean IC/TLC was 34.53 $\pm$ 1.79. Mean Epworth Sleepiness Score was 8.58 $\pm$ 0.96. 18 subjects were on LABA-ICS combination therapy. None of the subjects were taking a LABA in the absence of an ICS and vice versa. Fifteen subjects were taking tiotropium; 2 subjects were taking oral steroids at the time of the polysomnogram, and 1 subject was on theophylline. Five subjects had a history of cardiac disease.

We found significant univariate associations between sleep efficiency and AHI, IC/TLC, and SpO_2 nadir (Table 2), and IC/TLC was correlated with sleep efficiency (Figure 1). There was no relationship between FEV_1 and sleep efficiency. The relationship between IC/TLC and sleep efficiency was preserved in a multivariable regression model controlling for age, sex,

Table 2. Sleep deficiency data presented as univariable and multivariable correlation coefficients; $p \leq 0.05$ is considered statistically significant. Cardiac disease was defined as the presence of atrial fibrillation/flutter, coronary artery disease, and congestive heart failure

Variable	Univariable (β)	*P* Value	Multivariable (β)	*P* Value
Age, yr	−0.499	0.11	−0.236	0.54
Sex, male	2.08	0.74	−0.928	0.87
BMI, kg/m^2	−0.54	0.30	−0.339	0.52
FEV1 % predicted	0.098	0.57	−0.119	0.58
IC/TLC	0.654	0.03	1.13	0.02
AHI	−0.285	0.01	−0.322	0.01
SpO2 nadir	0.640	0.02	−0.043	0.89
LABA-ICS	8.85	0.15	13.31	0.04
Tiotropium	−1.88	0.76	−10.54	0.06
Theophylline	−5.65	0.74	−1.09	0.94
Oral steroid	11.83	0.34	−2.28	0.84
Cardiac disease	−5.78	0.48	−3.74	0.61

*BMI = body mass index; FEV1 = forced expiratory volume in 1 second; IC = inspiratory capacity; TLC = total lung capacity; AHI = apnea/hypopnea index; SpO2 nadir = overnight oxygen saturation nadir; LABA-ICS = Long-acting beta agonist and inhaled corticosteroid combination.

Table 3. Sleep latency data presented as univariable and multivariable correlation coefficients; $p \leq 0.05$ is considered statistically significant. Cardiac disease was defined as the presence of atrial fibrillation/flutter, coronary artery disease, and congestive heart failure

Variable	Univariable (β)	*P* Value	Multivariable (β)	*P* Value
Age, yr	0.388	0.50	0.173	0.80
Sex, male	−33.8	0.01	−29.76	0.03
BMI, kg/m^2	−0.005	0.10	0.393	0.71
FEV1 % predicted	−0.204	0.52	−0.025	0.96
IC/TLC	−1.440	0.01	−0.820	0.38
AHI	−0.124	0.57	0.032	0.89
LABA-ICS	2.94	0.80	−2.21	0.86
Tiotropium	−3.03	0.79	1.92	0.87
Theophylline	4.83	0.88	7.31	0.82
Oral steroid	−9.84	0.66	−10.14	0.69
Cardiac disease	24.92	0.09	12.09	0.52

*BMI = body mass index; FEV1 = forced expiratory volume in 1 second; IC = inspiratory capacity; TLC = total lung capacity; AHI = apnea/hypopnea index; LABA-ICS = Long-acting beta agonist and inhaled corticosteroid combination.

BMI, AHI, SpO_2 nadir, FEV_1, medications, and the presence of cardiac disease (Table 2). The association between SpO_2 nadir and sleep efficiency was no longer significant in the multivariable model, and LABA-ICS combination therapy was associated with increased sleep efficiency.

We also found significant univariate associations between sleep latency with IC/TLC and male sex (Table 3). However, in a multivariable regression model controlling for age, sex, BMI, AHI, FEV_1, medications, and cardiac disease, the relationship between IC/TLC and sleep latency was no longer significant. The inverse relationship between male gender and sleep latency remained significant in this model. There were no associations between FEV_1 and sleep latency in both univariable and multivariable analyses (Table 3).

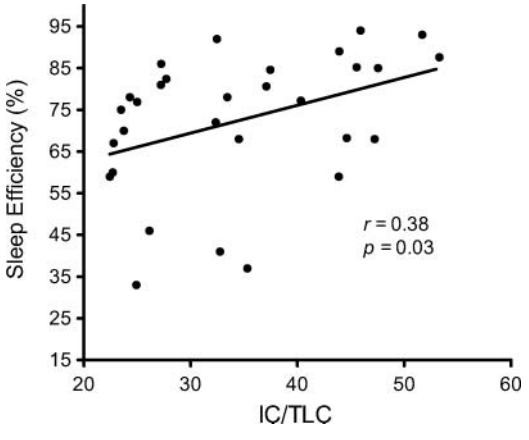

Figure 1. Scatter plot graph showing correlation between sleep efficiency and IC/TLC.

There were no significant associations between sleep efficiency and RV/TLC and T90. Arousal index was significantly associated with AHI but not with any pulmonary function variables, T90, or SpO_2 nadir.

DISCUSSION

Our study is the first to demonstrate that more severe lung hyperinflation, quantified by a reduced IC/TLC ratio, is associated with reduced sleep efficiency in patients with overlap syndrome, independent of apnea/hypopnea events. This relationship was also preserved after controlling for bronchodilator medications including theophylline and inhaled and oral steroids, as well as co-morbid cardiac disease, which is associated with sleep complaints and insomnia (17). We also found that greater lung hyperinflation is associated with longer sleep latency, although this relationship was not preserved in our multivariable model. Our findings suggest that more severe obstructive lung disease is associated with worse sleep quality. Previous studies have demonstrated an association between the presence of lung disease and poor sleep, however, FEV_1 has not been shown to correlate well with changes in sleep architecture (11).

Indeed, FEV_1 had no association with objective sleep quality in our study, and this suggests that FEV_1 is an inadequate measure of lung function as it relates to objective sleep quality in overlap syndrome patients. In fact, this is not exclusive to sleep given the numerous studies that have demonstrated the weak correlation of FEV_1 with other important outcomes in COPD (18–20).

Lung hyperinflation, on the other hand, has been shown to correlate with important functional outcomes, including mortality (13), and inspiratory capacity has been demonstrated to better correlate with exercise endurance than FEV_1 (21). Based on our findings, we propose that IC/TLC may be a better measure of

lung disease severity over FEV_1 in future studies investigating the association of lung function and sleep quality in overlap syndrome. We do not know why RV/TLC, another measure of hyperinflation, is not associated with reduced sleep efficiency in our study. In obese individuals, RV may be increased, and we speculate that this may impact the accuracy of RV/TLC as a marker for lung hyperinflation in the setting of obesity.

Potential mechanisms by which hyperinflation worsens sleep efficiency in overlap syndrome are uncertain. One possibility is that hyperinflation results in increased work of breathing, particularly in the recumbent position, which may disrupt sleep. Co-morbid insomnia is common in patients with COPD, and we speculate that increased lung hyperinflation may play a role in promoting insomnia in patients with overlap syndrome. (9)

A strong relationship between gender and sleep latency was observed in our study, and demonstrated that male gender was associated with shorter sleep latency. This is consistent with other studies that have found women generally have more difficulty falling asleep and have longer sleep latencies on diagnostic polysomnography (22–24). In addition, our study cohort is older, and postmenopausal women are at significantly higher risk for insomnia and sleep disturbances than younger women and men (25). In our study, longer sleep latency was associated with worse hyperinflation however this relationship was not preserved in our multivariable model.

Thus our findings suggest that lung hyperinflation has no significant impact on how long it takes to fall asleep for patients with COPD and co-existent OSA, although our study may be inadequately powered for this analysis. The mean Epworth Sleepiness Scale (ESS) for our cohort is within normal limits and argues against the presence of excessive sleepiness in our cohort. A previous study showed that COPD patients have normal mean sleep latencies on multiple sleep latency testing (26). This suggests patients with COPD are not at risk for excessive sleepiness. Perhaps this helps explain why the ESS did not correlate with any pulmonary function variables in our study (data not shown).

It is not known whether therapies aimed at reducing lung hyperinflation would improve sleep quality in patients with overlap syndrome. However, in patients with COPD without OSA, improving lung mechanics surgically improves sleep quality. The National Emphysema Treatment Trial (NETT) investigated whether lung volume reduction surgery (LVRS) improves lung function and mortality in patients with severe COPD compared to medical therapy alone (27). In this ancillary study, 16 patients had polysomnograms before and after LVRS (27). Investigators found that patients after LVRS had significant improvements in total sleep time and sleep efficiency compared to the medical therapy alone group which had no improvement (27). Although IC/TLC was not reported in this trial, LVRS has been reported to significantly reduce lung hyperinflation in other studies (28, 29).

Interestingly, our analysis also demonstrates that the use of long-acting beta agonists (LABA) and inhaled corticosteroid combination therapy is associated with increased sleep efficiency. Whether inhaled LABA-corticosteroid therapy has a favorable impact on sleep-centered outcomes in patients with COPD and overlap syndrome is unknown and warrants further study. This is in contrast to tiotropium, which did not have a significant impact on sleep efficiency in our study, consistent with previously published data (30). Finally, oral steroids and theophylline had no impact on sleep quality, but this may be due to the small number of subjects on these medications.

Weaknesses of our study include the retrospective design, small sample size, and lack of an intervention group. It is possible that hyperinflation is a marker for some other abnormality resulting in sleep disruption, such as gas exchange abnormalities, including nocturnal hypoxemia or hypercapnia (31–33). The effects of hypoxemia on sleep quality in patients with overlap syndrome are unknown. Our study did not find a relationship between nighttime oxygenation and sleep architecture. Another possible confounder is the presence of anxiety and depression, which are highly prevalent in patients with COPD (34).

However, the presence or absence of anxiety and depression could not reliably be determined in an objective way based on our chart review and was not included in the analysis. We chose to control for cardiac disease in our model due to the high prevalence of cardiac disease in COPD and OSA and its association with poor sleep (17). In addition, patient-centered outcomes such as quality of life, daytime functioning, and subjective measures of sleep quality were unable to be measured. We cannot, therefore, make any conclusions about how hyperinflation affects perceived sleep quality in overlap patients.

Another limitation of our study is that our subjects may not be representative of patients with overlap syndrome in a generalized population, and our findings may be vulnerable to ascertainment bias. The sleep-related complaints or problems that prompted obtaining the polysomnogram in these subjects are not controlled for in our analysis, and we do not know whether reduced sleep efficiency is associated with lung hyperinflation in patients without sleep complaints or problems. Furthermore, the health consequences of reduced sleep efficiency in this patient population are unknown. However, the significant associations between lung hyperinflation and sleep efficiency provide evidence that impaired lung mechanics negatively impact objective measures of sleep quality.

In conclusion, lower IC/TLC, a marker for more severe lung hyperinflation, is associated with reduced sleep efficiency in patients with COPD and co-existent OSA, independent of AHI. Our findings provide rationale to study potential mechanisms underlying this association and the possible sleep benefits of reducing hyperinflation in patients with overlap syndrome and other obstructive lung diseases.

Declaration of interest

Dr. Jeff Kwon and Dr. Brandon Lu have received grant support from GlaxoSmithKline Inc. and honoraria for services on an advisory board for Takeda Pharmaceuticals. Dr. Ravi Kalhan has received honoraria for service on the speakers' bureaus for GlaxoSmithKline, Boehringer-Ingelheim, Pfizer, and Astra-Zeneca as well as serving as a consultant to Boehringer-Ingelheim,

Takeda Pharmaceuticals, Astra-Zeneca, and Dey Pharmaceuticals. He has received grant support from GlaxoSmithKline. Dr. Lisa Wolfe has received honoraria for service on the speakers' bureaus for Hill- Rom and Cephelon as well as serving as a consultant to and has received grant support from ResMed.

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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