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Obstructive Sleep Apnea, Obesity, and the Development of Acute Respiratory Distress Syndrome

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SCIENTIFIC INVESTIGATIONS

Background: Obstructive sleep apnea (OSA) may increase the risk of respiratory complications and acute respiratory distress syndrome (ARDS) among surgical patients. OSA is more prevalent among obese individuals; obesity can predispose to ARDS.

Hypothesis: It is unclear whether OSA independently contributes towards the risk of ARDS among hospitalized patients.

Methods: This is a pre-planned retrospective subgroup analysis of the prospectively identified cohort of 5,584 patients across 22 hospitals with at least one risk factor for ARDS at the time of hospitalization from a trial by the US Critical Illness and Injury Trials Group designed to validate the Lung Injury Prediction Score. A total of 252 patients (4.5%) had a diagnosis of OSA at the time of hospitalization; of those, 66% were obese. Following multivariate adjustment in the logistic regression model, there was no significant relationship between OSA and development of ARDS (OR = 0.65, 95%CI = 0.32-1.22). However, body mass index (BMI) was associated with subsequent ARDS development (OR = 1.02, 95%CI = 1.00-1.04, p = 0.03). Neither OSA nor BMI affected mechanical ventilation requirement or mortality.

Conclusions: Prior diagnosis of OSA did not independently affect development of ARDS among patients with at least one predisposing condition, nor the need for mechanical ventilation or hospital mortality. Obesity appeared to independently increase the risk of ARDS.

Keywords: obstructive sleep apnea, obesity, acute respiratory distress syndrome

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Acute respiratory distress syndrome remains a common cause of respiratory failure in intensive care units (ICU) with estimated mortality rate of over 40%.[1,2] Given limited treatment options once the condition develops, the investigative paradigm is shifting towards identifying potential predisposing conditions and implementation of secondary prevention strategies.[3] While increased body mass index (BMI) may represent a predisposing factor for ARDS development,[4] it is still unclear whether the closely associated condition, obstructive sleep apnea (OSA), independently contributes towards the risk of ARDS.

OSA is a growing health concern with prevalence estimates ranging between 3% to 24% in the general population.[5,6] Similar rate of about 25% has been reported in surgical patients.[7] OSA has been associated with an increased risk for the development of ARDS among patients undergoing surgery. In the largest review, of over 6,000,000 cases of orthopedic and general surgery procedures, 2.5% and 1.4% of patients had a diagnosis of OSA, respectively. The authors found that OSA was associated with a higher odds ratio (OR) of developing ARDS: 2.39 for orthopedic and 1.58 for general surgery cases.[8] A recent meta-analysis of thirteen trials reported a significant association of OSA and development of acute respiratory failure in surgical patients.[9] OSA was found to be an independent risk factor for post-obstructive pulmonary edema in patients requiring tracheostomy.[10] Patients with OSA requiring surgery have been shown to have a higher rate of pulmonary complications[11-13] with hypoxemia being most common,[14-17] even following adjustment for BMI.[14,17]

BRIEF SUMMARY

Current Knowledge/Study Rationale: OSA and obesity are known risk factors for respiratory complications/ARDS following surgery. It is unclear whether OSA independently contributes towards the risk of ARDS among all hospitalized patients.

Study Impact: Among patients with at least one predisposing condition, diagnosis of OSA prior to hospitalization did not independently affect the risk of progression to ARDS. Obesity appeared to independently increase the risk of ARDS.

Perhaps the most challenging part in clarifying the potential role of OSA on predisposition to develop ARDS is to tease out any independent effect of obesity on ARDS as up to 94% of patients requiring bariatric surgery may have a concomitant diagnosis of sleep apnea.[18] While some studies indicate that a higher BMI may confer an increased risk of ARDS,[4,19] others reported a lower rate of ARDS among obese patients.[20]

Since the treatment of ARDS is significantly limited once the condition is established, the mission of the US Critical Illness and Injury Trials Group - Lung Injury Prevention Study (USCIITG-LIPS) investigators has been to identify modifiable risks for ARDS and potential strategies to prevent its occurrence. Given the high prevalence of OSA in general population, we

aimed to better define the association between OSA and ARDS. To date, there have not been any studies specifically examining the effect of OSA diagnosis on the subsequent development of ARDS among patients at risk. Additionally, we aimed to better define the interrelationship between OSA, obesity, and ARDS. To explore this, we performed a secondary analysis of a large prospective cohort of patients requiring hospitalization to estimate the risk of pre-hospital diagnosis of OSA, as well as obesity, on the development of ARDS.

METHODS

The USCIITG investigated 5,584 patients admitted to 22 hospitals in order to evaluate the Lung Injury Prediction Score (LIPS).[3] With the exception of three centers, all data was collected prospectively. The study protocol was approved by the Institutional Review Board at each participating location. The current study is a pre-planned subgroup analysis of the prospectively identified LIPS cohort and was approved by the LIPS ancillary committee.

Study Population

Details of the study population have been previously described.[3] Inclusion criteria were adult patients (> 18 years) who had at least one major risk factor for ARDS including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or major cardiac and lung surgery. Exclusion criteria were acute lung injury (ALI) at the time of admission, transfer from an outside hospital, death in the emergency department, comfort or hospice care, or hospital readmission during the study period.[3]

Predictor Variables

The primary exposure of interest was a diagnosis of OSA documented in the medical record on admission, obtained from the "history and physical" form or directly from the patient or family members. The secondary pertinent exposure, BMI, was calculated based on admission height and weight. We stratified BMI into the following categories, as previously reported:[4] underweight (BMI < 18.5 kg/m^2), normal (BMI 18.5-24.9), overweight (BMI 25-29.9), obese (BMI 30-39.9), and severely obese (BMI > 40).

Information on severity of OSA and compliance with therapy was not collected. Demographic and clinical information were obtained at the time of hospital admission or preoperatively at the time of surgery. These data were used to calculate the LIPS score as a measure of the baseline risk of developing ARDS, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score as a measure of disease severity.[3]

Outcome Variables

The main outcome was the development of ARDS during the hospitalization. At the time of data collection, the presence of ALI/ARDS was determined by the Standard American-European consensus conference criteria: development of acute, bilateral pulmonary infiltrates and hypoxemia (PaO_2/FiO_2 < 300 – ALI, PaO_2/FiO_2 < 200 – ARDS) in the absence of clinical signs of left atrial hypertension.[21] However, since recent Berlin definition[22] removed the term ALI and reclassified hypoxemia in the range of PaO2/FiO2 < 300 as ARDS, we use that term in reporting our results. Secondary outcomes included the need for invasive mechanical ventilation and mortality. Patients were followed for the duration of their hospital stay, up to 90 days.[3]

Statistical Analyses

Patients were separated into two groups on the basis of whether they had documented diagnosis of OSA at the time of hospital admission or not. We first performed univariate analysis to compare demographics, comorbidities, and medications between two groups. Each of the systematically collected clinical variables obtained in the LIPS database was compared between those with diagnosis of OSA and the rest of the cohort. We then determined the (unadjusted) OR of developing ARDS for patients with history of OSA compared to others. Contingency variables were compared using Fisher exact test, and the distribution of continuous variables was assessed with the t-test; ANOVA was used for multiple comparisons. We also performed univariate analysis examining each of the BMI categories and their respective unadjusted associations to ARDS.

Multivariate analyses using a logistic regression model were performed to determine the adjusted OR of developing ARDS. Similar analyses were repeated to evaluate the two exploratory secondary outcome variables. Covariates included the LIPS and the APACHE II scores, BMI, OSA, age, smoking status, alcohol use, cardiac surgery, brain injury, congestive heart failure NYHA stage IV, diabetes, pneumonia, chronic obstructive pulmonary disease, asthma, gastroesophageal reflux disease, aspiration, use of angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, statins, and inhaled steroids. The BMI variable was used in the initial logistic regression model as continuous variable and in the subsequent model we used four dummy variables per previously reported BMI cutoffs.

Risk assessments are reported as OR with 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant. All analyses were performed using JMP Pro 10.0.2 statistical software (SAS Institute Inc., Cary, NC).

RESULTS

As previously described, 5,584 patients were enrolled into the LIPS study between March and August of 2009.[3] The median age of the entire cohort was 57 years, and the majority was Caucasian and male. Of those patients, 252 (4.7%) had documented diagnosis of OSA at the time of hospitalization. Incidence of ARDS was 7.5% and 6.7 % (p = 0.61) for patients with and without a diagnosis of OSA, respectively. Univariate analysis showed that patients with OSA were more likely to be older, Caucasian, undergo cardiac and brain surgery, have diabetes, chronic pulmonary disease, and reflux. Those patients were also more likely to be on aspirin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin, proton pump inhibitor, hypoglycemic medication, and inhaled steroids. They had higher LIPS score and BMI and abused tobacco less frequently (**Table 1**). No baseline differences in APACHE II scores were present. Notably, 66% of OSA patients were obese (BMI > 30) compared to only 28% of those without the diagnosis of OSA (p < 0.001).

Table 1—Group characteristics

Parameter	OSA (n = 252)	No OSA (n = 5,332)	p-value
Age [a]	59 ± 14.7	56 ± 18.8	0.007
Gender (Male)	57%	56%	0.83
Caucasian	67.5%	60.9%	0.04
BMI [a]	36.7 ± 10.8	27.5 ± 7.2	< 0.001
Active Smoking	14%	24%	< 0.001
Alcohol use	30%	29%	0.83
APACHE II [a]	10.3 ± 6.1	9.7 ± 6.5	0.16
LIPS [a]	3.5 ± 2	3.1 ± 2.1	0.003
Comorbidities/Risk Factors			
Cardiac Surgery	17.5%	9.3%	< 0.001
Aortic Surgery	2.8%	2.2%	0.58
Thoracic Surgery	1.2%	3.2%	0.07
Emergency Surgery	5.9%	6.0%	0.9
Acute Abdomen	4.0%	5.3%	0.3
Spine Surgery	14.3%	8.4%	0.003
Bone Fractures	2.0%	6.1%	0.006
Brain Injury	3.5%	9.1%	0.003
Lung Contusion	0.8%	3.5%	0.02
High Risk Trauma	6.3%	18%	< 0.001
CHF, NYHA IV	4.4%	3.2%	0.32
Sepsis	29.0%	32.7%	0.22
Shock	4.4%	7.3%	0.07
Diabetes	44.4%	22.2%	< 0.001
Pneumonia	26.6%	21.9%	0.08
COPD	19%	10.1%	< 0.001
Asthma	14.3%	7.6%	< 0.001
Comorbidities/Risk Factors (*continued*)			
ILD	1.2%	0.9%	0.6
GERD	25%	12.0%	< 0.001
Aspiration	3.17%	3.83%	0.73
Pancreatitis	5.6%	5.8%	0.8
Chest Radiation	0.8%	1.3%	0.48
Solid Cancer	4.0%	5.2%	0.4
Leukemia	0.4%	1.1%	0.3
Lymphoma	0.8%	1.6%	0.3
Hemodialysis	5.9%	3.8%	0.09
Cirrhosis	1.6%	2.2%	0.48
Medications			
ACEI	21.4%	8.3%	< 0.001
ARB	13.5%	5.1%	< 0.001
Statin	42.5%	24.5%	< 0.001
Aspirin	40.9%	26.4%	< 0.001
Amiodarone	1.2%	0.9%	0.6
PPI	32.1%	22.5%	< 0.001
H2 Blocker	7.5%	5.2%	0.1
Insulin	19.8%	9.6%	< 0.001
Oral Hypoglycemic	18.7%	10.8%	< 0.001
Inhaled β-agonist	24.6%	13.1%	< 0.001
Steroids, inhaled	21.4%	8.3%	< 0.001
Steroids, systemic	11.9%	8%	0.03
Chemotherapy	1.2%	3.2%	0.07
Admission from Home	81%	80%	0.8

OSA, obstructive sleep apnea; APACHE, Acute Physiology and Chronic Health Evaluation; LIPS, lung injury prediction score; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; GERD, gastroesophageal reflux disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PPI, proton-pump inhibitor. [a] Mean ± standard deviation. T-test used for continuous variables, and the Fisher exact test for contingency tables.

We included the following variables in the logistic regression model based on abovementioned statistically significant group differences and clinical importance: age, Caucasian, active smoking, alcohol use, LIPS, APACHE 2, cardiac surgery, brain injury, congestive heart failure New York Heart Association class IV, diabetes mellitus, pneumonia, aspiration, chronic obstructive lung disease, asthma, reflux, statin, aspirin, inhaled steroid use, sleep apnea, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, BMI. Following multivariate adjustment in the logistic regression model, there was no observed significant association between OSA and development of ARDS (OR = 0.65, 95% CI = 0.32-1.22). However, there appeared to be significant association of BMI (as a continuous variable) with subsequent ARDS development, with an OR of 1.02 (95% CI = 1.00-1.04, p = 0.03) per single unit increase in BMI (1 kg/m^2), which translates into estimated overall increase in risk of 22% for an increase in BMI by 10 units. However, when we stratified patients who developed ARDS into categories of BMI, greater BMI was associated with even greater risk of ARDS (**Table 2**). With regards to secondary outcomes, there were no significant differences in requirement for mechanical ventilation or an effect on mortality based on prior diagnosis of OSA (**Table 3**); there was also no significant association with BMI.

DISCUSSION

This is the first study to specifically evaluate the role of OSA in the development of ARDS among at-risk patients in a prospectively collected cohort. Initial unadjusted analysis revealed no difference in incidence of ARDS for patients with OSA compared to controls; however, obesity portended a greater risk. Following multivariate adjustment in logistic regression, there was no significant difference in incidence of ARDS between those with and without OSA diagnosis, nor was there a difference in the need for mechanical ventilation or mortality. Overall, higher BMI was associated with an increased risk of ARDS in the logistic regression model.

It is not surprising that we found a significant association between BMI and ARDS, as increased risk has been demonstrated previously.[4,19] However, we could not replicate in our study previously reported risk of ARDS among patients with OSA. Given prevalence of obesity among patients with OSA, lack of a statistical association may be confounded by the rate

Table 2—Relationship between BMI and ARDS across BMI categories in the logistic regression model

BMI categories	% ARDS [a] (N with ARDS/overall N for BMI category)	p-value [b]	OR (CI) [b]
< 18.5	7.53% (18/239)	0.47	1.25 (0.65-2.26)
18.5-24.9	5.8% (88/1518)		
25-29.9	6.24% (188/3013)	0.077	1.37 (0.97-1.94)
30-30.9	8.57% (93/1085)	0.053	1.43 (0.99-2.07)
> 40	9.6% (31/322)	0.053	1.69 (0.98-2.8)

[a] χ^2 value = 0.026 for BMI effect across groups on univariate analyses. [b] Values from logistic regression model examining effects of OSA and other covariates on the risk of ARDS.

Table 3—OSA and the risk for respiratory complications and death in the entire cohort and following adjustment by logistic regression

Outcome	OSA N = 252	No OSA N = 5,332	Univariate: p	LR: OR, CI, p
ARDS	7.5%	6.7%	0.61	0.65, (0.32-1.22), 0.21
MV	33.8%	34.3%	0.88	0.96, (0.65-1.39), 0.81
Mortality	3.1%	5.2%	0.15	0.42, (0.12-1.12), 0.09

%, % of subjects in the exposure group having the respective outcome; numerator, count of outcome; denominator, total count of exposure group; OR, odds ratio; CI, confidence interval; OSA, obstructive sleep apnea; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation.

of underdiagnosis of OSA in hospital and general population. Among surgical patients, of the 661 individuals who screened high risk for OSA, 81% did not have a prior diagnosis in one study.[7] Others demonstrated that known OSA diagnosis was missed by surgeons and anesthesiologists in 58% and 15% of cases, respectively; when the remaining patients were administered polysomnography prior to surgery, 37.7% were found to have moderate to severe OSA.[23] For the general population, current prevalence estimates of moderate to severe sleep disordered breathing are 10% among 30- to 49-year-old men; 17% among 50- to 70-year-old men; 3% among 30- to 49-year-old women; and 9% among 50- to 70-year-old women.[24,25] Therefore, given average age (57) in our study population, the reported rate of diagnosed OSA of 4.7% in our cohort most likely underestimates the actual prevalence of OSA in those patients. Association between OSA and ARDS may have been further weakened by OSA treatment patients may have been receiving prior to admission.

Sixty-six percent rate of obesity in OSA patients in our study is consistent with recent reports.[26] In examining why obese patients may have had higher incidence of ARDS, we reviewed ventilator data and found no significant differences in delivered tidal volumes, peak, and plateau pressures between patients with BMI greater and less than 30. We were not able to retrospectively report data on transpulmonary pressures as this was not routinely done at all participating centers. It is possible that insufficient PEEP relative to transpulmonary pressure in obese individuals may have contributed to atelectrauma. With regards to rates of pneumonia as a potential contributor, documented incidence of pneumonia was lower in patients with BMI > 30 compared to controls, so pneumonia could also not explain increased incidence of ARDS in obese subjects. Moreover, we have not found any difference in the rate of aspiration between the two groups. Interestingly, a higher prevalence of obese subjects with diabetes in the OSA group did not translate into an expected reduction in lung injury as previously described.[27] Therefore, other mechanisms may have played a role in observed findings.

Obese patients may experience such alterations in pulmonary mechanics as airflow obstruction, decreased lung volumes, and impaired gas exchange, all of which may predispose them to develop ARDS.[28] Additionally, adipose tissue is an active endocrine organ secreting bioactive molecules called adipokines. Obesity is characterized by an overproduction of proinflammatory adipokines (leptin, resistin) and a lower production of anti-inflammatory adipokines (adiponectin).[29] Additionally, obesity is associated with an increase in formation of reactive oxygen species (ROS).[30] However, since many of those with OSA are not obese,[31] mechanisms of OSA effect on propensity to develop ARDS may be both interdependent and independent of those described in obesity.

OSA also represents a pro-inflammatory state with increased levels of IL-6 and IL-8[32]; higher IL-8 levels are associated with increased risk of development of acute lung injury.[33] Others observed an increase in KL-6 levels in patients with more severe OSA.[34,35] Elevation of KL-6 has previously been reported in patients with lung injury and found to predict poorer outcomes.[36-38] Additionally, OSA with its intermittent hypoxia and reoxygenation is thought to represent a state akin to chronic ischemia-reperfusion with increased ROS formation during restoration of oxygenation[29]; pro-inflammatory cytokine profile observed in OSA has been consistent with response to oxidative stress.[39] OSA is also characterized by increased leptin levels with correlation found not only for BMI but also for apnea-hypopnea index and reduced adiponectin levels.[40-42]

Overall, it appears that there is a significant overlap between effects of obesity and OSA; and short of a prospective trial thoroughly screening for OSA on admission and then examining ARDS incidence across body weight categories and OSA severity while taking into account other confounding factors, it would be difficult to separate relative contributions of each.

Our study has several important limitations. Although a secondary analysis, it was pre-planned at the time of conception of the LIPS investigation. OSA was most likely underdiagnosed in our study population, as we relied only upon the information available at the time of hospital admission, thereby limiting potential inferences of its effect on studied outcomes. Additionally, we did not have data on OSA severity and compliance with CPAP therapy and therefore cannot separate the effect of treated and untreated OSA. This is important because CPAP therapy could negate the potential risk inherent in OSA and protect against ARDS. For those reasons and given a preponderance of obese OSA individuals in our cohort we separately examined the effect of BMI on ARDS and assessed the role of different BMI categories. Nonetheless, this study adds to the limited body of research into the role of OSA on the likelihood of developing ARDS. The strengths of the study include

its multi-centered design and a large number of patients at risk for ARDS. Additionally, all patients in the cohort were systematically characterized as having or not having OSA specifically at admission, and followed subsequently for the development of ARDS. Given the potential overlap in mechanisms of lung effects with obesity, our study emphasizes the need to improve OSA screening in future ARDS prevention trials because in order to truly define the role of OSA, one needs to ensure that it is adequately ascertained as well as characterized (severity, compliance) among study participants.

CONCLUSIONS

Prior diagnosis of OSA did not affect development of ARDS among patients with at least one predisposing condition, nor did it affect the need for mechanical ventilation or hospital mortality. However, obesity appeared to independently increase the risk of ARDS.

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