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High Risk for Obstructive Sleep Apnea Hypopnea Syndrome Predicts New Onset Atrial Fibrillation after Cardiac Surgery: A Retrospective Analysis

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Abstract

Purpose: Obstructive sleep apnea hypopnea syndrome (OSAHS) is highly prevalent in patients undergoing coronary artery bypass surgery (CABG). OSAHS is a risk factor for the development of atrial fibrillation (AF) but the risk of AF in patients who are high-risk for OSAHS is unclear.

Methods: A retrospective study was conducted on consecutive patients undergoing CABG from 2013-2015 without AF pre-operatively. Patients were categorized as low-risk for OSAHS, high-risk for OSAHS, or diagnosed OSAHS based on medical records review. All diagnosed OSAHS patients were on active treatment with positive airway pressure. Outcomes assessed were postoperative AF (POAF), postoperative length of stay, re-intubation, in-hospital mortality and cost of hospitalization.

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Ethical approval: For this type of study formal consent is not required.

Results: Out of 209 eligible patients, 66.5% were low-risk for OSAHS, 18.7% high-risk for OSAHS, and 14.8% diagnosed/treated for OSAHS. POAF developed in 96 patients (45.9%) with greater frequency in high-risk OSAHS patients (69.2% high-risk, 41.9% low-risk, 40.3% diagnosed/treated, $p=0.01$). In analyses adjusted for age, sex, ethnicity and comorbidities, high-risk for OSAHS was associated with 2.9 greater odds (95% CI [1.2, 7.3], $p=0.02$) for POAF while diagnosed/treated OSAHS was not associated with elevated risk (OR=1.4, 95% CI [0.6, 3.6], $p=0.50$) compared to patients at low risk for OSAHS.

Conclusions: High risk for OSAHS is an independent predictor for POAF in patients undergoing CABG. In contrast, patients diagnosed and treated for their OSAHS are not at elevated risk of POAF. These findings support evaluation of a standardized OSAHS screening and treatment program as part of the pre-operative evaluation for elective CABG.

Keywords

Sleep Apnea; Coronary Artery Bypass Graft Surgery; Mortality; Length of Stay; Cost; Atrial Fibrillation; Screening

Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS), a syndrome characterized by repetitive collapse of the upper airway during sleep, is extremely common with recent estimates of prevalence in adults ranging from 9% to 38% [1]. However, it is estimated that up to 90% of people with OSAHS are undiagnosed [2], likely owing to poor awareness of OSAHS [3], lack of routine screening, and limited access to diagnostic testing [4]. OSAHS is highly prevalent in patients referred for coronary artery bypass graft (CABG) surgery [5] and is a potential risk factor for postoperative atrial fibrillation (POAF) [6]. A meta-analysis of prospective cohort studies reported that OSAHS increases the odds of POAF approximately 2-fold [6] and increases health care burden by increasing morbidity and mortality, especially after CABG [7]. However, there is a lack of evidence for evaluating the risk of new-onset POAF and potential adverse outcomes after cardiac surgery. Such adverse outcomes include re-intubation, prolonged length of stay, and in-hospital mortality among the patients who are clinically undiagnosed but are at high risk for OSAHS. Our study was aimed to determine the effects of undiagnosed but high risk for OSAHS on outcomes of cardiac surgery, especially on the development of new-onset POAF.

Methods

Study Design, Definition, and Protocol

We conducted a retrospective study of all 305 hospitalized patients who underwent CABG surgery at Western Reserve Health Education/NEOMED, Northside Medical Center, Ohio from January 2013 to March 2015. We excluded patients less than 18 years of age, pregnant or prisoners at the time of surgery and those with a prior history of atrial fibrillation. All CABG patients were identified by ICD 9 procedure code of 36.1 (bypass anastomosis for heart revascularization). All data were abstracted from manual review of the hospital electronic medical record (EMR) and in triplicate by three different abstractors. Where discrepancies were identified, records were reviewed by a fourth reviewer who adjudicated

differences. This analysis was approved by the Western Reserve Health Education Institutional Review Board with a waiver of patient consent.

Information on baseline variables such as age, sex, ethnicity, body mass index (BMI), history of smoking, loud snoring, Mallampati score and information on common co-morbidities including hypertension, coronary artery disease, congestive heart failure, stroke, diabetes mellitus, thyroid disorders, chronic obstructive pulmonary disease and chronic kidney disease were extracted through review of the EMR. Perioperative characteristics including use of beta blockers in the perioperative period, pre-operative cardiac function including left ventricular ejection fraction, number of graft vessels, type and previous history of cardiac surgery were similarly collected. All information was obtained during the inpatient visit. No information was collected after discharge. Body mass index (BMI) was divided into four categories using standard clinical cut-points as per the World Health Organization (WHO) classification of the degree of obesity (BMI < 25.0 kg/m² - normal weight, BMI 25.0 to 29.9 kg/m² - overweight, BMI 30.0 to 39.9 kg/m² - obese, BMI ≥ 40 kg/m² - morbidly obese). Mallampati score was divided into two categories (<3 and ≥3).

High risk for OSAHS was defined by the presence of three or more of the following five criteria: age > 65 years, hypertension, a presence of loud snoring, BMI ≥ 35 kg/m² and Mallampati score ≥ 3. Individual components of these criteria have been previously defined as indicators for moderate to severe OSAHS. We used components such as age, sex, BMI and snoring from STOP-BANG questionnaires as those risk factors were independent predictors of high risk for OSAHS in previous literature [8]. We also added Mallampati score in our tool, as it also independently predicted the high-risk for OSAHS [9]. Review of standardized anesthesiology pre-operative notes that queried specifically on a prior diagnosis of OSAHS and use of positive airway pressure (PAP) therapy was performed to obtain prior OSAHS history. All cases of diagnosed OSAHS received perioperative treatment with positive airway pressure (either continuous or bilevel PAP).

The primary outcome of our study was the development of POAF and the secondary outcomes were postoperative LOS, reintubation rates, in-hospital mortality and hospitalization cost after CABG surgery. POAF was defined as new onset of AF without any previously known history of AF including on pre-operative ECG. We reviewed physician notes in the EMR to identify the new diagnosis of AF. All diagnoses were verified by review of 12-lead EKGs. Postoperative LOS was defined as the duration of hospital stay from CABG surgery to hospital discharge. Hospitalization cost was acquired from the hospital billing system which was not adjusted according to latest consumer price index. Patients who were reintubated after initial extubation, secondary to any cause were included in reintubation rates.

Statistical Methods

Unadjusted differences between OSAHS groups (low-risk, high-risk, diagnosed and treated) were compared using chi-squared tests, unpaired t-tests or Wilcoxon rank sum tests as appropriate. Multivariable logistic regression was used to identify independent predictors of POAF. To evaluate the relationship between OSAHS status and POAF, three separate models were derived. The base model (Model 1) included OSAHS status, age, sex and ethnicity.

Model 2 included all variables included in the base model and obesity, hypertension, coronary artery disease, thyroid disorders and chronic kidney disease. Model 3 included all variables included in model 2 and congestive heart failure, diabetes and chronic obstructive pulmonary disease. A two-sided p-value < 0.05 was used to define statistical significance. All analyses were conducted using SAS v. 9.4 (Cary, NC).

Results

Baseline Demographics

Out of a total of 305 patients undergoing CABG between January 2013 and March 2015, 58 patients were excluded secondary to the presence of atrial arrhythmias before surgery and 5 were excluded due to being prisoners at the time of surgery. An additional 33 patients were removed from the final study sample because of incomplete information available on outcomes and/or important baseline characteristics (Figure 1). Demographic characteristics of the remaining 209 patients are shown in Table 1. Overall the population was of median age of 67 years and predominantly male (73.2%) with a high prevalence of traditional cardiac risk factors including hypertension (84.7%), obesity (44.5%), diabetes (41.2%) and active or previous history of smoking (68.0%). Of the 209 patients, 139 (66.5%) were at low risk for OSAHS, 39 (18.7%) were at high risk for OSAHS and 31 (14.8%) were previously diagnosed with OSAHS. All previously diagnosed OSAHS patients reported ongoing treatment with PAP. Compared to the low-risk OSAHS group, the high risk and diagnosed OSAHS groups were older, had greater BMI and greater co-morbidity burden including hypertension, obesity, congestive heart failure, stroke and diabetes. (Table 1)

Most of the patients received a beta blocker in the perioperative period, especially postoperatively. The mean cardiac left ventricular ejection fraction was 52.5%. Overall, 41% of patients had four or more vessels bypassed, 40% had 3 vessels bypassed, and 19% had only one or two vessels bypassed. The majority (81%) of patients had isolated CABG versus 19% had CABG combined with valve surgery. Sixteen percent of patients had a previous history of cardiac surgery. (Table 1)

Outcomes

Primary Outcome—Out of 209 patients, new onset POAF occurred in 96 (45.9%) patients. POAF was more common in the high-risk OSAHS group compared to both the diagnosed and treated OSAHS and low-risk OSAHS groups, while rates were comparable in the latter two groups (69.2% vs 41.9% vs 40.3% respectively, $p=0.01$ for an overall test of homogeneity). In multivariable models, after adjusting for age, sex, ethnicity and other comorbidities, OSAHS status remained an independent risk factor for POAF (Table 2). Those at high-risk for OSAHS had statistically significant 2.9 higher odds of POAF (95% CI [1.2, 7.3], $p=0.02$) than low-risk OSAHS patients while those with treated and diagnosed OSAHS had an OR of 1.4 (95% CI [0.6, 3.6], $p=0.50$).

Secondary Outcomes—As shown in Table 1, re-intubation rates were higher in both those with diagnosed OSAHS (12.9%) and those at high risk for OSAHS (10.3%) compared to the rate in those who were low risk for OSAHS (5.8%), but these differences were not

statistically significant. In-hospital mortality rates were higher in those diagnosed with OSAHS (3.2%) or at high risk for OSAHS (5.1%) compared to low-risk for OSAHS (0.7%), but this trend did not reach statistical significance. In unadjusted analyses (Table 3), post-operative LOS was 2.9 days longer in those who were at high-risk for OSAHS compared to low-risk for OSAHS ($p=0.02$). After adjustment for age, sex, ethnicity, obesity, hypertension, coronary artery disease, thyroid disorders, and chronic kidney disease, this difference decreased to 2.3 days which was no longer statistically significant ($p=0.09$). Hospitalization costs were not significantly greater in either diagnosed OSAHS or high-risk OSAHS groups compared to the low-risk OSAHS group in both unadjusted and adjusted analyses (Table 3).

Discussion

Previously published literature has established that a diagnosis of OSAHS is an independent risk factor for new onset of POAF after CABG surgery [6, 10] and our results assert the same. However, the impact of high risk but undiagnosed OSAHS on development of POAF has been unclear. Our findings demonstrate that the incidence of POAF following CABG surgery is significantly higher in patients who are at high risk for OSAHS, compared to those who are at low risk. In fact, such incidence is higher even compared to patients with a prior diagnosis of OSAHS (69.2% vs. 41.9%). The increased risk compared to previously diagnosed OSAHS is likely related to the fact that all of our previously diagnosed patients were on active treatment with PAP therapy. Another important finding is that the prevalence of high-risk OSAHS among those undergoing CABG was substantially higher than previously diagnosed OSAHS (18.7% vs. 14.8%). These findings are in line with previous studies demonstrating a high prevalence of undiagnosed OSAHS at the time of surgery [11–13]. These results regarding the high prevalence of high risk yet undiagnosed OSAHS provide the opportunity to potentially improve outcomes by increasing recognition and treatment of OSAHS pre-operatively. Of note, the overall prevalence of POAF in our study (22.4%) was in line with the prevalence of this complication in prior studies [6,7,14].

Previous research has demonstrated OSAHS to be a strong predictor of AF after elective CABG [6] as well as a risk factor for recurrent AF after both electro-cardioversion [13] and radiofrequency ablation [15]. Several pathophysiological processes have been proposed for development of AF secondary to OSAHS. In patients with OSAHS, hypoxia, hypercapnia and increased sympathetic drive may all predispose to AF [16,17]. Furthermore, dramatic shifts in atrial transmural pressures occur due to forceful ventilatory efforts during obstructive apneas [18,19]. These acute changes in pressure result in dilation of the atria and triggering stretch-activated atrial ion channels which may promote AF [20]. Furthermore, OSAHS also independently increases markers of systemic inflammation which has been directly associated with increased incidence of AF [21,22]. These mechanisms may interact with specific post-CABG triggers such as incomplete revascularization, intra-cardiac catheters and use of inotropic agents to further increase the risk of AF [6].

Although OSAHS has been previously shown to be an independent predictor of AF after CABG [6,7], the POAF risk in patients who are high risk for OSAHS but yet undiagnosed is unclear. In a small study of 128 patients screened for OSAHS with the Berlin questionnaire

[23], the prevalence of POAF in high risk vs. low risk patients was similar (10.8% vs 8.3%, $p=0.21$). Of note, the overall prevalence of POAF was low in this cohort which limits the power to detect an effect of OSAHS. Van Oosten et al. [7] reported the POAF risk was elevated 2.2-fold in those with either diagnosed or at high risk for OSAHS compared to low risk OSAHS. However, the study did not separately report risks in those with previously diagnosed OSAHS from those at high risk. Furthermore, the independent risk attributable to OSAHS risk is unclear as the study did not account for many differences in comorbidities between those groups. Moore et al. [12] reporting on a cohort of 121 patients found that an oxygen desaturation index ≥ 5 /hour predicted greater risk of POAF but again this study did not completely account for potentially important confounders. Our analysis of a fairly generalizable cohort of patients undergoing CABG found those without a diagnosis of OSAHS but at high risk on clinical grounds had the highest risk for POAF compared to both those at low risk as well as those with diagnosed and treated OSAHS. These data not only support an elevated risk from undiagnosed OSAHS but also may suggest treatment with CPAP can reduce this risk.

According to Kanagala et al. [24], the risk of AF recurrence in untreated OSAHS patients after electro-cardioversion doubles and treatment with CPAP therapy attenuates that risk. Furthermore, in OSAHS patients, treatment with positive airway pressure can reverse cardiac remodeling [25]. Our results suggest a similar effect in the peri-operative period around CABG. Further prospective studies are needed to validate that CPAP can reduce the POAF risk in OSAHS patients undergoing CABG and the duration of CPAP use needed to lower this risk. Similar to prior large patient population studies [14, 26–29], our study also showed that advanced age and male sex were strong predictors of new onset POAF.

Previous studies were not able to demonstrate any effects of high-risk OSAHS on hospital length of stay in CABG patients. However, they have shown a significantly prolonged LOS when comparing high risk and previously diagnosed OSAHS patients together versus low risk patients (6.5 vs 5.3 days, $p=0.006$) [7]. Our study used postoperative LOS instead of total LOS to reduce potential confounding of additional pre-operative testing or stabilization of patients prior to surgery. We found a significant 2.9 day increase in post-operative LOS in high risk OSAHS patients compared to low risk patients in unadjusted analyses which dropped to 2.3 days after a multivariable adjustment. Our findings raise the possibility that improved screening and care of OSAHS in high risk patients may decrease hospital stay. Our data also suggested statistically non-significant higher hospitalization costs for both high-risk and diagnosed OSAHS patients, when compared to low-risk patients, however, we were clearly underpowered for this outcome. Larger prospective studies should be able to better assess the extent to which OSAHS screening and treatment may be cost-saving.

There are several limitations to this study. First, the retrospective nature of this analysis relied on data available in the electronic medical record. This limited the data available to classify OSAHS risk and led us to utilize a risk measurement tool that has not been directly validated although each of the components has been shown to predict OSAHS risk. Second, prior diagnosis of OSAHS and use of PAP therapy was based on self-report with no objective assessment of PAP adherence. Third, we were unable to record the influence of preoperative cardiac function on outcomes and to collect the number of POAF episodes,

including recurrence rates or treatment success rates or hemodynamic compromise because of POAF. Finally, because of the observational nature of the study, we cannot exclude the potential of unmeasured confounders contributing to our findings. Despite these limitations, our study is to date, the first study to demonstrate high risk of OSAHS to be an independent predictor for the development of new-onset POAF after CABG.

Conclusions

This study demonstrates that patients undiagnosed but at high-risk for OSAHS have a nearly three-fold greater odds of developing new-onset POAF following CABG compared to patients with low risk. No significant elevation in risk was observed in patients with prior diagnosis of OSAHS and treated with PAP. These data suggest that the post-operative complications such as POAF may be avoided by a more standardized OSAHS screening and treatment program for patients undergoing elective CABG. Large prospective studies to identify the optimal screening instrument and a patient population who might benefit from peri-operative PAP therapy are needed to further test this hypothesis.

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Figure 1:
Study Sample Selection

Table 1:

Demographic and Clinical Characteristics of patients undergoing CABG by sleep apnea status

Characteristics	Low-risk OSAHS (N=139)	High-risk OSAHS (N=39)	Diagnosed OSAHS (N=31)	Overall (N=209)	P-value
Demographic Characteristics					
Age (years) *	66 (59, 76)	72 (67, 76)	67 (59, 72)	67 (60, 76)	0.03
Sex (%)					0.76
Male	74.1	74.4	67.7	73.2	
Female	25.9	25.6	32.3	26.8	
Race (%)					0.65
Caucasian	92.1	92.3	96.8	92.8	
Non-Caucasian	7.9	7.7	3.2	7.2	
BMI (%)					<0.01
Normal	29.5	5.1	9.7	22.0	
Overweight	39.6	23.1	19.4	33.5	
Obese	28.8	35.9	32.3	30.6	
Morbidly obese	2.2	35.9	38.7	13.9	
Smoking Status (%)					0.01
Active Smoker	28.2	20.9	50.0	29.2	
Previous Smoker	32.2	51.2	37.5	36.8	
Non-Smoker	39.4	27.9	12.5	34.0	
Loud snoring (%)	10.1	33.3	22.6	16.3	0.01
Mallampatti score					<0.01
<3	87.1	38.5	32.3	75.1	
>=3	13.0	61.5	67.7	24.9	
Co-morbidities (%)					
Obesity	30.9	71.8	71.0	44.5	<0.01
Hypertension	80.6	97.4	87.1	84.7	0.03
CAD	65.5	74.4	83.9	69.9	0.10
CHF	13.0	20.5	32.3	17.2	0.03
Stroke	6.5	15.4	25.8	11.0	0.01
Diabetes	30.9	59.0	64.5	41.2	0.01
Thyroid Disorders	13.7	18.0	25.8	16.3	0.24
COPD	11.5	12.8	22.6	13.4	0.26
CKD	13.0	7.7	25.8	13.9	0.08
Dialysis	1.4	2.6	6.5	2.4	0.25
Perioperative variables					
Beta blocker use prior to surgery (%)	63.3	82.1	87.1	70.3	0.01
Beta blocker use after surgery (%)	95.7	100	93.6	96.2	0.33
Cardiac Ejection Fraction (Mean, SE)	52.4 (1.1)	52.7 (2.1)	52.7 (1.9)	52.5 (0.9)	0.94

Characteristics	Low-risk OSAHS (N=139)	High-risk OSAHS (N=39)	Diagnosed OSAHS (N=31)	Overall (N=209)	P-value
No. CABG vessels (%)					0.02
1	8.6	20.5	16.1	12.0	
2	4.3	7.7	19.4	7.2	
3	44.6	35.9	25.8	40.2	
>=4	42.5	35.9	38.7	40.7	
Type of open heart surgery (%)					0.02
CABG alone	86.3	69.2	71.0	80.9	
CABG ± Valve	13.7	30.8	29.0	19.1	
History of prior cardiac surgery (%)	9.4	15.4	48.4	16.3	<0.01
Outcomes (%)					
New onset Atrial Fibrillation	40.1	69.2	41.9	45.9	0.01
In-Hospital Mortality	0.7	5.1	3.2	1.9	0.17
Reintubation rates	5.8	10.3	12.9	7.7	0.32

* values in median (quartile1, quartile3)

BMI: Body Mass Index; CKD: Chronic Kidney Disease; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; CABG: Coronary Artery Bypass Graft; OSAHS: Obstructive Sleep Apnea Hypopnea Syndrome

Table 2:

Predictors of post-operative atrial fibrillation following coronary artery bypass graft surgery.

Odds ratios for development of post-operative atrial fibrillation *			
Variables	Model 1	Model 2 (Model 1 + obesity, Hypertension, CAD, Thyroid disorders, CKD)	Model 3 (Model 2 + Diabetes, COPD, CHF)
High-risk vs Low-risk OSAHS	2.9 (1.3- 6.6), p=0.01	3.1 (1.3-7.6), p=0.01	2.9 (1.2-7.3), p=0.02
Diagnosed/Treated vs Low-risk OSAHS	1.4 (0.6-3.3), p=0.43	1.5 (0.6-3.7), p=0.43	1.4 (0.6-3.6), p=0.50
Age (per 10-year increment)	2.1 (1.6-2.9), p<0.01	2.0 (1.5-2.8), p<0.01	2.1 (1.5- 2.9), p<0.01
Male vs Female	2.2 (1.1-4.4), p=0.03	2.4 (1.2-5.0), p=0.02	2.6 (1.2-5.4), p=0.01
Caucasians vs Non-Caucasians	0.94 (0.3-3.1), p=0.91	0.97 (0.3-3.4), p=0.96	1.0 (0.3-3.4), p=0.95
Model C-Statics	0.73	0.76	0.76

* Values represent adjusted odds ratio, with 95% confidence intervals and p values. Unadjusted Odds ratio for High-risk vs Low-risk OSAHS 3.33 (1.56-7.13), p=0.01; and for Diagnosed/Treated vs low-risk OSAHS, 1.07 (0.49-2.35), p=0.87.

Model 1 is adjusted for age, sex, race, and OSAHS status.

Model 2 is adjusted for variables of Model 1, and other variables, such as obesity, hypertension, CAD, Thyroid disorders, CKD.

Model 3 is adjusted for all variables of model 2, and other variables, such as diabetes, COPD and CHF.

OSAHS: Obstructive Sleep Apnea Hypopnea Syndrome; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure.

Table: 3

Association of OSAHS status with Postoperative length of stay and hospitalization costs in patients undergoing coronary artery bypass graft surgery

Outcome	Unadjusted	Adjusted for age, sex, ethnicity, obesity, hypertension, coronary artery disease, thyroid disorders, chronic kidney disease
Postoperative Length of Stay (days)		
High-risk vs Low-risk OSAHS	2.9 (0.4, 5.4), p=0.02	2.3 (-0.4, 5.0), p=0.09
Diagnosed/Treated vs Low-risk OSAHS	2.2 (-0.6, 4.9), p=0.12	2.5 (-0.4, 5.3), p=0.09
Cost of Hospitalization (US dollars)		
High-risk vs Low-risk OSAHS	47200 (-6258, 100629), p=0.08	42500 (-14901, 99948), p=0.15
Diagnosed/Treated vs Low-risk OSAHS	44500 (-13593, 103569), p=0.13	50000 (-10700, 110766), p=0.11

OSAHS: obstructive sleep apnea hypopnea syndrome. Mean estimate (95% confidence interval) reported for each covariate along with p-value from pairwise contrast.