CHEST

Sleep Apnea Increases the Risk of New Hospitalized Atrial Fibrillation

A Historical Cohort Study

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OBJECTIVES: This study examined the relationship between newly diagnosed OSA and incident hospitalized atrial fibrillation (AF) over the subsequent 10 years in a large arrhythmia-free cohort.

METHODS: Adults referred between 1994 and 2010 to a large academic hospital with suspected OSA who were arrhythmia-free at the time of the first diagnostic sleep study were included. Clinical data were linked to provincial health administrative data to define outcome. Cox regressions were used to investigate the relationship between severity of OSA as measured by the apnea-hypopnea index (AHI) and degree of nocturnal hypoxemia, and incident hospitalized AF.

RESULTS: In total, 8,256 subjects were included in this study. Their median age was 47 years, 62% were men; 28% had an AHI > 30 events per hour, and 6% spent > 30% of sleep time with oxygen saturation < 90%. Over a median follow-up of 10 years (interquartile range, 7-13 years), 173 participants (2.1%) were hospitalized with AF. Controlling for age, sex, alcohol consumption, smoking status, previous heart failure, COPD, and pulmonary embolism, nocturnal hypoxemia (but not AHI) was a significant predictor of incident AF: hazard ratio, 2.47 (95% CI, 1.64-3.71). After further controlling for BMI and hypertension, this association was attenuated but remained significant (hazard ratio, 1.77 [95% CI, 1.15-2.74]).

CONCLUSIONS: In a large arrhythmia-free clinical cohort with suspected OSA, nocturnal hypoxemia was independently associated with a 77% increased hazard of incident hospitalized AF. These findings further support a relationship between OSA, nocturnal hypoxemia, and new-onset AF, and they may be used to enhance AF prevention in patients with OSA and severe nocturnal hypoxemia. CHEST 2018; 154(6):1330-1339

KEY WORDS: atrial fibrillation/flutter; prognosis; sleep apnea syndromes

ABBREVIATIONS: AF = atrial fibrillation; AHI = apnea-hypopnea index; CHF = congestive heart failure; CIF = cumulative incidence function; HR = hazard ratio; MI = myocardial infarction; PAP = positive airway pressure; PSG = polysomnography; SaO_2 = oxygen saturation

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Atrial fibrillation (AF) is the most common chronic arrhythmia in adults, resulting in significant morbidity and mortality.[1] A number of studies have implicated OSA as a possible independent risk factor for AF.[2-4] OSA might predispose to AF through a number of mechanisms: hypoxemia, hypercapnia, nocturnal hypertension, oxidative stress, intrathoracic pressure fluctuations, sympathetic activation, chronic inflammation, and endothelial dysfunction. All these factors predispose subjects to electrical and structural heart remodeling over time.[5-8]

Supporting a causal link between OSA and AF, treatment of OSA with CPAP has been found to reduce the risk of recurrent AF.[9,10] However, there is a paucity of research examining the longitudinal relationship between OSA and incident AF.[11-14] The findings have been inconsistent, possibly due to variability in the criteria used to diagnose OSA and the small number of severe OSA cases included in community-based studies.

In a large cohort of patients who underwent full night diagnostic sleep studies, the present study sought to evaluate the longitudinal relationship between OSA and incident hospitalized AF. We have previously shown that sleep-related oxygen desaturation is a stronger predictor of cardiovascular events and all-cause mortality than the apnea-hypopnea index (AHI) in this cohort[15]; the present study therefore specifically examined the relationship of OSA, evaluated by using AHI and degree of nocturnal hypoxemia.

Patients and Methods

Study Design

This historical cohort study was conducted by using clinical and polysomnographic (PSG) data on all adults referred with suspected OSA who underwent a first diagnostic sleep study (level 1 PSG) at a large urban academic hospital (Toronto, Ontario, Canada) between 1994 and 2010. These data were probabilistically linked to provincial health administrative databases from 1991 to 2015 at the ICES (details are given in e-Appendix 1).

The ethics committees of all institutions involved (St. Michael's Hospital and Sunnybrook Health Sciences Centre) approved the study.

Data Sources

Clinical Data: Information on demographic, clinical, and PSG characteristics have been consistently collected at St. Michael's Hospital sleep laboratory since 1991 (technical specifications for PSG are provided in e-Appendix 1). Details on the variables collected are reported elsewhere.[15]

Provincial Health Administrative Data: Ontario is the most populous province in Canada, with a population of > 13 million. It has a universal single-payer health-care system that covers all medically necessary services, including most of the cost of the different types of positive airway pressure (PAP) devices (ie, continuous, autotitrating, and bilevel) that are used to treat sleep apnea through the Assistive Devices Program. Copies of high-quality administrative datasets[16,17] on publicly funded services including individual-level information on physician claims, hospitalization, and ED visits are housed at ICES.[18] A description of the ICES datasets is available at https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx. The full dataset creation plan is available from the authors upon request.

Study Population

Individuals who had undergone a first diagnostic sleep study (index date) during the study period, and who had a diagnosis of OSA (AHI ≥ 5 events per hour) or suspected OSA (referred with sleep apnea but with AHI < 5 events per hour), were extracted from the St. Michael's Hospital database. Patients were excluded if they had > 50% central respiratory events, or AHI < 5 events per hour and a diagnosis of another sleep disorder.[15]

Individuals with any physician diagnosis of arrhythmia prior to the index date (since 1991) were excluded. Physician-diagnosed arrhythmias were defined as: (1) any inpatient hospitalization with any diagnosis for arrhythmia per *International Classification of Diseases, Ninth Revision,* codes (427 except 427.6: atrial fibrillation and atrial flutter, ventricular fibrillation, cardiac arrest, paroxysmal tachycardia, and other cardiac arrhythmias [but not premature beats]) and *International Classification of Diseases, Tenth Revision,* codes (I47-49: paroxysmal tachycardia, atrial fibrillation and flutter, and other cardiac arrhythmias); (2) any outpatient visit with a physician billing diagnostic code of 427 (arrhythmias, cardiac, other). We made our definition of prior arrhythmias as all-encompassing as possible to maximize sensitivity.

Exposure

The exposure of interest was OSA severity based on AHI and percentage of sleep time spent with oxygen saturation (SaO_2) < 90%.

Using AHI, OSA was categorized as mild (AHI of 5-14.9 events per hour), moderate (AHI of 15-30 events per hour), or severe (AHI >

those of the Canadian Institute for Health Information. Severity of comorbidities at baseline was approximated by using an aggregated score, the Johns Hopkins' Aggregated Diagnosis Groups categories (The Johns Hopkins ACG System, Version 10). G. H. has received research support as the Sir John and Lady Eaton Professor and Chair of Medicine, Department of Medicine, University of Toronto. T. K. was supported by the Canadian Respiratory Research Network Fellowship Training Award. Funding for training of graduate students and new investigators within the Network was supported by grants from the following: the Canadian Institutes of Health Research–Institute of Circulatory and Respiratory Health; Canadian Lung Association/Canadian Thoracic Society; British Columbia Lung Association; and Industry Partners Boehringer-Ingelheim Canada Ltd., AstraZeneca Canada Inc., Novartis Canada Ltd., and GlaxoSmithKline Inc.

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30 events per hour).[19] Details on the AHI definition[20] are given in e-Appendix 1.

The percentage of sleep time spent with $SaO_2 < 90\%$ was divided into quartiles, and severe nocturnal hypoxemia was defined as > 30% of the sleep time with $SaO_2 < 90\%$.[21,22] In addition, the apnea-hypopnea duration (mean and maximum) was considered in secondary analyses.

Outcomes

The study's primary outcome was time from the index date to first hospital admission with a diagnosis of AF or atrial flutter. Definition of AF was based on *International Classification of Diseases, Ninth Revision* (427.3), and *International Classification of Diseases, Tenth Revision* (I48), codes that were previously validated against electrocardiograms and medical records associated with electrocardiograms.[23,24]

The study's secondary outcomes were as follows: (1) hospitalization with the most responsible diagnosis for admission for AF/atrial flutter; and (2) a composite outcome that included any hospitalization or ED visit with a diagnosis of AF or atrial flutter.

Study participants were followed up until first hospitalization with AF, death, or March 31, 2015, whichever occurred first.

Covariates and Risk Factors

The following potential confounders were considered: traditional cardiovascular risk factors[25] such as sex, age, BMI, smoking, income status, alcohol consumption, and baseline comorbidities (hypertension, diabetes, COPD, stroke, pulmonary embolism/infarction, myocardial infarction [MI], and congestive heart failure [CHF]). Given that information on PAP acceptance, but not adherence, was available, patients were considered as treated since the time of their claim for a PAP device in the Assistive Devices Program[26] database from 2000 onward. Demographic characteristics, BMI, and smoking status were derived from clinical data, whereas income status, alcohol dependency/intoxication, and other comorbidities were derived from health administrative data.

A detailed list and definitions of variables derived from health administrative data are provided in e-Table 1.

Analyses

Descriptive statistics were used to characterize the study cohort. Because AF has been shown to be associated with an increased risk of death,[27] death is a competing event (ie, it may preclude hospitalization for AF or alter the chances to observe it), which could result in a biased estimate according to the Kaplan-Meier method.[28,29] We therefore estimated the incidence of AF hospitalizations according to OSA severity by using the cumulative incidence function, which accounts for the competing risk of death. Univariate and multivariable Cox regression models were used to investigate the association between OSA and incident AF. The results are expressed as hazard ratios (HRs) and 95% CIs.[30] The proportional hazards assumptions for each variable were tested.[30,31]

Anticipating a relatively small number of AF hospitalizations in the follow-up time, the number of variables included in the statistical model was restricted to avoid overfitting. The following known AF-related risk factors were selected a priori based on literature review[32-34] and expert opinion: age, sex, smoking status, alcohol dependency/intoxication, previous CHF, COPD, and pulmonary embolism/infarction. Because there are possible causal relationships between OSA and hypertension[35] and obesity,[36] these two factors may be part of the causal pathway between OSA and AF.[37] Thus, including hypertension or BMI in a statistical model may diminish a true association. To examine this theory, hypertension, BMI, and receipt of PAP treatment as time-dependent covariates were added to the model in the secondary analyses. A priori-defined interactions between exposures and sex and age were also tested.

In the secondary analyses, to compare with other studies,[13,14] the AHI and sleep time spent with $SaO_2 < 90\%$ as variables with skewed distributions for which nonlinearity was observed were natural log-transformed; they were then used in the regression models as a continuous variable.

Given a recent finding that central sleep apnea but not OSA was a predictor of incident AF,[12] our main model was refitted on the subsample of individuals who had central AHI < 5 events per hour. To exclude the possibility that nocturnal hypoxemia might be a reflection of underlying cardiopulmonary disease, we also refitted our main statistical model on the subsample without COPD or CHF at baseline. Fine and Gray competing-risk regressions were used to account for the competing risk of death.[38]

All statistical analyses were performed in the secure environment of ICES following Ontario privacy standards using R version 2.15.2 (R Foundation for Statistical Computing; www.r-project.org).

Results

Population Characteristics

Of 10,149 subjects in the original linked cohort,[15] a total of 1,893 (18.7%) individuals were excluded because of a previous arrhythmia diagnosis, leaving 8,256 arrhythmia-free individuals for inclusion in the present analyses. Their median age was 47 years, and 62% were men (Table 1). The median AHI was 15 events per hour (interquartile range, 6-33 events per hour), with substantial variability in disease severity: 1,844 (23%) had no OSA (AHI < 5 events per hour), whereas 2,263 (28%) had severe OSA (AHI > 30 events per hour). Severe hypoxemia (defined as > 30% of total sleep time with $SaO_2 < 90\%$) was present in 463 (5.6%). Compared with the original cohort, these arrhythmia-free individuals were younger, with less severe OSA, and had fewer comorbidities at baseline.

OSA and Incident Hospitalized AF

Over a median follow-up of 10 years (interquartile range, 7-13 years), 173 of 8,256 participants (2.1%) were hospitalized with AF. Those with incident AF events were older, more likely to be male, have a higher

TABLE 1] Participants' Characteristics at Baseline: Total Sample and According to Subsequent Hospitalization With AF/Atrial Flutter

Characteristic	Total Sample (N = 8,256)	Hospitalized With AF in Follow-up Time	
		No (n = 8,083)	Yes (n = 173)
Demographic characteristics			
Age, median (IQR), y	47 (38-56)	47 (38-56)	63 (53-70)
Male sex	5,122 (62)	4,992 (62)	130 (75)
BMI, median (IQR), kg/m^2	28.8 (25.2-33.3)	28.7 (25.2-33.2)	31.5 (27.8-35.7)
SES by income status			
Quintile 1	1,622 (20)	1,579 (20)	43 (25)
Quintile 5	2,336 (29)	2,285 (29)	51 (30)
Smoking Status, No. (%)			
Current	1,598 (21)	1,563 (21)	35 (23)
Ex	1,408 (19)	1,366 (18)	42 (27)
Never	4,585 (60)	4,507 (61)	78 (50)
Alcohol dependency/intoxication	490 (5.9)	474 (5.9)	16 (9.2)
Prior comorbidities			
Hypertension	2,475 (30.0)	2,371 (29.3)	104 (60.1)
Myocardial infarction	156 (1.9)	144 (1.8)	12 (6.9)
Congestive heart failure	163 (2.0)	146 (1.8)	17 (9.8)
Revascularization procedures	167 (2.0)	159 (2.0)	8 (4.6)
Diabetes	984 (11.9)	934 (11.6)	50 (28.9)
Cancer	335 (4.1)	316 (3.9)	19 (11.0)
COPD	805 (9.8)	750 (9.3)	55 (31.8)
Asthma	1,402 (17.0)	1,363 (16.9)	39 (22.5)
Level of comorbidities per ADG category			
Low	2,631 (32)	2,595 (32)	36 (21)
Moderate	3,446 (42)	3,380 (42)	66 (38)
High	2,179 (26)	2,108 (26)	71 (41)
OSA-related symptoms			
ESS total, 0-24, median (IQR)	8 (5-12)	8 (5-12)	8 (5-11)
Snore, yes	6,792 (88)	6,647 (87)	145 (91)
Witnessed apnea, yes	3,230 (43)	3,161 (43)	69 (47)
Daytime sleep, yes	2,943 (38)	2,852 (38)	91 (58)
Polysomnographic characteristics, median (IQR)			
TST, h	5.8 (5.0-6.5)	5.8 (5.0-6.5)	5.1 (4.3-5.9)
Sleep efficiency, %	82.6 (71.1-89.8)	82.8 (71.4-89.9)	72.90 (58.8-83.0)
Total arousal index, events per hour	22.3 (13.5-37.1)	22.2 (13.4-37.0)	29.3 (17.9-44.1)
Total PLMI, events per hour	0.8 (0.0-11.4)	0.8 (0.0-11.2)	7.6 (0.0-30.0)
Total AHI, events per hour	14.9 (5.7-32.9)	14.8 (5.6-32.6)	22.3 (7.8-41.2)
Central AHI, events per hour	0.2 (0.0-1.0)	0.2 (0.0-1.0)	0.4 (0.0-2.8)
Mean SaO_2 in TST, %	95.0 (93.6-96.1)	95.0 (93.7-96.1)	93.7 (91.7-94.8)
Percent of TST spent with $SaO_2 < 90\%$	0.1 (0.0-2.2)	0.1 (0.0-2.1)	1.9 (0.1-18.6)
Sleep time spent with $SaO_2 < 90\%$, min	0.4 (0.0-7.3)	0.3 (0.0-6.9)	5.7 (0.4-49.1)

Data are presented as No. (%), unless otherwise indicated. Numbers may not add to total because of missing values. ADG = aggregated diagnosis groups (The Johns Hopkins ACG System, Version 10); AF = atrial fibrillation; AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; IQR = interquartile range; PLMI = periodic leg movement index; SaO_2 = oxygen saturation; SES = socioeconomic status; TST = total sleep time.

BMI, be current or ex-smokers, and have more comorbidities at baseline (e-Table 2, Table 1). Among 576 individuals (7%) who died during follow-up, 507 died (88%) without being hospitalized with AF, and 69 individuals (12%) died following a hospitalization for AF. The cumulative incidence of hospitalized AF at 10 years was 3.2% (95% CI, 2.4-4.1) for individuals with severe OSA (AHI > 30 events per hour) compared with 1.7% (95% CI, 1.3-2.1) for those without severe OSA (AHI ≤ 30 events per hour) and 7.8% (95% CI, 5.2-10.4) for individuals with severe hypoxemia (SaO_2 < 90% for >30% of sleep time) compared with 1.7% (95% CI, 1.4-2.1) for those with milder or no hypoxemia (Figs 1, 2).

In univariate analyses, significant dose-response relationships were observed between incident hospitalized AF and our two exposures (Table 2). Severe OSA (AHI > 30 events per hour) was associated with an HR of 2.64 (95% CI, 1.67-1.41) compared with no OSA (AHI < 5 events per hour), whereas severe nocturnal hypoxemia (SaO_2 < 90% for > 30% of the night) was associated with an HR of 4.76 (95% CI, 3.30-6.87) compared with milder or no hypoxemia. After controlling for age, sex, alcohol consumption, smoking status, previous CHF, COPD, and pulmonary embolism, the association between AHI > 30 events per hour and incident AF was no longer statistically insignificant (HR, 1.29 [95% CI, 0.79-2.11]). In contrast, the adjusted relationship between severe nocturnal hypoxemia and AF remained significant (HR, 2.47 [95% CI, 1.64-3.71]). After additionally controlling for hypertension, BMI, and PAP treatment acceptance, the association was

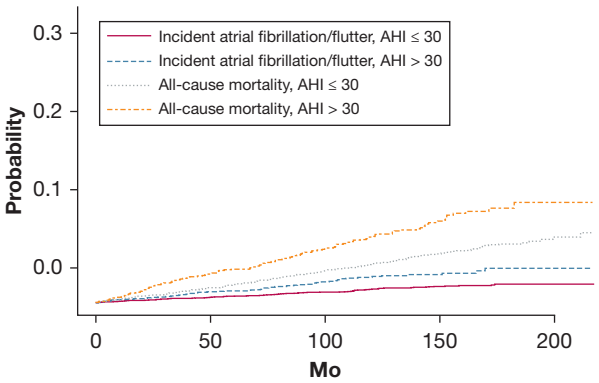

Figure 1 – *Estimated cumulative incidence of incident hospitalized atrial fibrillation/flutter and all-cause mortality by severity of obstructive sleep apnea as measured by the AHI. AHI = apnea-hypopnea index.*

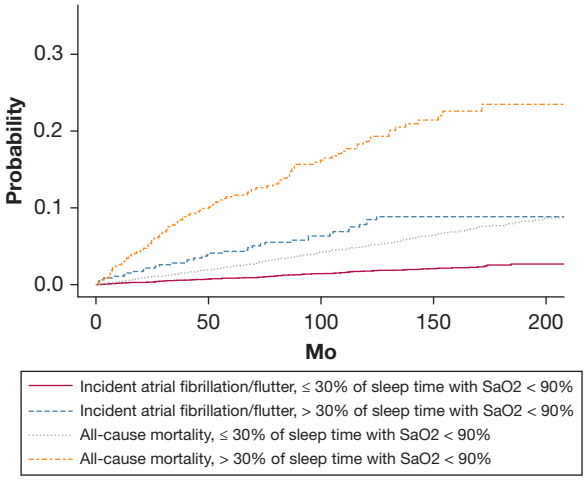

Figure 2 – *Estimated cumulative incidence of incident hospitalized atrial fibrillation/flutter and all-cause mortality according to severity of nocturnal hypoxemia. SaO_2 = oxygen saturation.*

further attenuated (HR, 1.87 [95% CI, 1.24-2.83]) but remained significant (Fig 3).

The association between nocturnal oxygen desaturation and AF was stronger in women compared with men, and among those aged < 65 years compared with those aged ≥ 65 years (*P* values for interaction < .05).

Results were similar after controlling for the competing risk of death, limiting the analyses to patients without COPD or CHF at baseline and to those with central AHI < 5 events per hour, and for the secondary outcomes (e-Tables 3-8). Only the obstructive apnea duration was significantly associated with the primary outcome in the univariate analysis; this association became nonsignificant controlling for confounders (e-Table 9).

Discussion

In a large, clinical, arrhythmia-free cohort of individuals with suspected OSA, 2.1% of individuals experienced incident hospitalized AF over a median 10 years of follow-up. Our incidence rate of 210 per 100,000 person-years was lower than that previously reported.[13,14] This cohort may have a lower risk for AF because participants were younger, with lower BMI, and included a smaller proportion of men. In addition, younger individuals in Ontario have been shown to be less likely to be hospitalized for AF than their older counterparts.[39] Although both measures of OSA severity (an increase in AHI and percentage of sleep time spent with oxygen desaturation) were associated with incident AF in

TABLE 2] Association Between OSA Severity as Measured by the AHI and the Degree of Nocturnal Oxygen Desaturation and Hospitalizations With AF/Atrial Flutter

Exposure	No. of Events/No. of Participants	Univariable	Model 1	Model 1 + Treatment[a]	Model 1 + BMI + Hypertension	Model 1 + BMI + Hypertension + Treatment[a]
As measured by the AHI (events/h)						
5 ≤ AHI < 15	38/2,260	1.34 (0.81-2.21)	1.01 (0.59-1.72)	0.93 (0.56-1.54)	0.90 (0.52-1.55)	0.83 (0.50-1.40)
15 ≤ AHI ≤ 30	39/1,823	**1.86 (1.13-3.07)**	1.22 (0.72-2.07)	1.02 (0.60-1.72)	0.97 (0.57-1.67)	0.80 (0.47-1.37)
AHI > 30	66/2,263	**2.64 (1.67-4.17)**	1.29 (0.79-2.11)	1.06 (0.63-1.80)	0.86 (0.51-1.44)	0.73 (0.43-1.26)
AHI < 5	26/1,844	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
AHI > 30	66/2,263	**1.92 (1.41-2.62)**	1.19 (0.85-1.67)	1.08 (0.76-1.54)	0.91 (0.64-1.29)	0.87 (0.61-1.26)
AHI ≤ 30	103/5,927	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
As measured by the degree of nocturnal oxygen desaturation						
% of TST spent with SaO_2 < 90%						
[0.01, 0.42)	24/1,361	1.65 (0.99-2.76)	1.09 (0.63-1.88)	1.09 (0.65-1.83)	0.88 (0.50-1.56)	0.88 (0.51-1.50)
[0.42, 4.02)	35/1,569	**2.19 (1.38-3.47)**	1.28 (0.79-2.07)	1.19 (0.75-1.89)	1.00 (0.61-1.65)	0.96 (0.60-1.55)
[4.02, 100.0]	76/1,631	**4.70 (3.18-6.93)**	**2.04 (1.33-3.11)**	**1.96 (1.30-2.95)**	1.33 (0.84-2.10)	1.36 (0.87-2.12)
0.00	38/3,690	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
% of TST spent with SaO_2 < 90%						
> 30	36/463	**4.76 (3.30-6.87)**	**2.47 (1.64-3.71)**	**2.45 (1.67-3.60)**	**1.77 (1.15-2.74)**	**1.87 (1.24-2.83)**
≤ 30	137/7,788	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Data are presented as hazard ratios (95% CIs). Statistically significant values are in bold. Model 1 (main model) = age, sex, alcohol dependency/intoxication, smoking status, previous heart failure, COPD, and pulmonary embolism/infarction. See Table 1 legend for expansion of abbreviations.

[a]Acceptance of positive airway pressure treatment as time-dependent covariate.

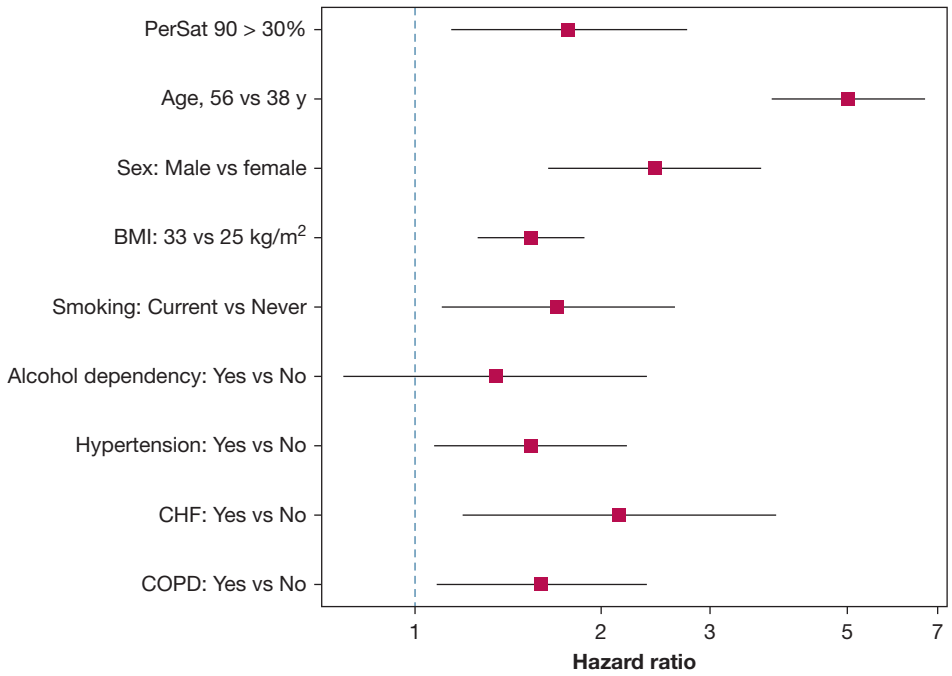

Figure 3 – *Results from multivariable Cox regression model presented as standardized hazard ratios (comparing 75th percentile with 25th percentile). CHF = congestive heart failure; PerSat90 = percentage of sleep time spent with oxygen saturation < 90%.*

univariate analysis, only nocturnal oxygen desaturation was independently associated with increased risk of new-onset AF controlling for confounders. This outcome suggests that nocturnal hypoxemia could be a mechanistic link in the relationship between OSA and AF.

There is growing evidence from animal and human studies that the pathophysiologic acute and chronic effects of OSA, which include hypoxemia, predispose to AF via the electrical and structural remodeling that occurs over time.[5-8] Intermittent hypoxemia may enhance arrhythmogenesis through shortening of the effective refractory period,[40] increasing catecholamine sensitivity,[41] and causing myocardial structural changes.[42,43]

Our nocturnal hypoxemia findings are consistent with two other clinic-based studies.[13,14] Similar to the study performed by Gami et al,[14] nocturnal oxygen desaturation, but not AHI, was an independent predictor of subsequent incident hospitalized AF. Our study and that of Gami et al used the so-called "Chicago" definition of hypopnea,[20] which does not require oxygen desaturation to define an event. In contrast, Cadby et al[13] found an association between both AHI and oxygen desaturation with incident hospitalized AF but used an alternative scoring criteria to define hypopneas (obstructive events needed to be associated with a > 3%-4% oxygen desaturation to be classified as a hypopnea). The ability of AHI to predict cardiovascular consequences has been found to improve with an increased degree of oxygen desaturation required to define hypopneas.[44] Together, these findings underscore the potential importance of nocturnal hypoxemia in mediating cardiovascular risk from OSA and raise the question of whether a more direct measure of variability and severity of nocturnal hypoxia might be even more predictive than AHI.

Our findings indicate that nocturnal hypoxemia imparts a greater risk of incident AF in women than in men, and in those aged < 65 years compared with those older. These findings are consistent with those of previous studies,[11,14] suggesting that these groups, who are typically at somewhat lower risk of AF, might be especially vulnerable to the effects of OSA and hypoxemia.

The present study has several potential strengths and limitations. We used the same PSG scoring criteria over

time. Our cohort included individuals with a wide range of OSA severity and a relatively large number of female subjects. We matched a high percentage of individuals (89%) to health administrative data, which provided us with long and near complete follow-up to derive outcomes. Although health administrative data were collected retrospectively, clinical data were collected for research purposes prospectively with standardized protocols in place. The traditional AF risk factors, including older age, male sex, obesity, hypertension, previous COPD, and CHF, were also predictive of hospitalized AF in the study cohort, lending face validity to our model.

As with any observational study design, there are limitations related to availability of data on important confounders (eg, treatment adherence, left atrial size, presence of obesity hypoventilation syndrome, congenital or valvular heart disease). However, it is well known that adherence to PAP treatment is generally low.[45,46] Furthermore, even assuming a protective effect of PAP, inability to adjust for PAP usage would bias our results toward the null. The generalizability of our findings may be limited by the single-center study design and use of Ontario residents only. Our findings are limited to hospitalized AF, which may represent a different phenotype of AF compared with asymptomatic and nonhospitalized AF.

Given the strong association we found between hypoxemia and incident AF, it is perhaps surprising that therapeutic supplemental oxygen has not been found to be as effective as CPAP in reducing BP in patients with OSA. However, it is by no means clear that all cardiovascular complications arising from OSA are brought about by the same mechanisms.[47] OSA-related hypertension might be caused more by sympathetic overactivity than hypoxemia. Furthermore, it is possible that more severe hypoxemia is a marker for OSA that is more severe in other respects, such as greater swings in intrathoracic pressure, in which case it is unlikely that supplemental oxygen would be helpful. Finally, we are not advocating that hypoxemia be targeted therapeutically with oxygen supplementation. CPAP remains the gold standard for treating OSA, and the intent of our study is to indicate those at highest risk of developing AF.

We cannot exclude the possibility that nocturnal oxygen desaturation in the patients in our study was related to underlying cardiopulmonary disease such as CHF and COPD. However, our cohort was relatively healthy and young, and the association between nocturnal hypoxemia and incident AF hospitalization remained significant, although attenuated, after controlling for the presence of CHF, COPD, smoking status, and other comorbidities. When patients with CHF and COPD were completely excluded from the analysis, the association remained significant controlling for age, sex, alcohol consumption, smoking status, and pulmonary embolism/infarction but became nonsignificant additionally controlling for BMI and hypertension. Given our results on the effect of hypoxemia independent of number and length of respiratory events, it is possible that nocturnal hypoxemia increases the risk of AF more in these groups (synergistic effect) due to the underlying abnormal cardiac substrate that is already prone to arrhythmia.

Finally, we had insufficient power to perform subgroup analyses and to consider all available confounders and risk factors in our statistical model as well as interaction terms. Other potential limitations of this cohort are discussed elsewhere.[15]

Conclusions

In a large clinical cohort with suspected OSA and free of any arrhythmias at baseline, severe nocturnal hypoxemia ($SaO_2 < 90\%$ for 30% of sleep time) was an independent predictor of incident hospitalization for AF. These findings support a relationship between OSA, chronic nocturnal hypoxemia, and the development of AF, and may be used to identify those patients with OSA who are at greatest risk of developing AF.

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Author contributions: All co-authors were involved in the following: study conception and design, interpretation of data, revising the dataset creation plan and the manuscript critically for the accuracy and important intellectual content, and final approval of the version to be published. T. K. additionally was involved in the following: literature search, obtaining administrative data, analyses of data, and drafting of the manuscript. A. S. G. additionally was involved in the applications for the ethics boards and obtaining administrative data. R. S. L. additionally was involved in the applications for the ethics boards and drafting of the manuscript, and is a custodian of the sleep laboratory dataset from which the study sample was extracted. R. S. L., A. S. G., and T. K. had access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The lead author, R. S. L., affirms that the present article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Additional information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

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