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Risk of new-onset atrial fibrillation in elderly patients with the overlap syndrome: a retrospective cohort study

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Abstract

Objective Co-existence of obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) is referred to as overlap syndrome. Overlap patients have greater degree of hypoxia and pulmonary hypertension than patients with OSA or COPD alone. Studies showed that elderly patients with OSA alone do not have increased risk of atrial fibrillation (AF) but it is not known if overlap patients have higher risk of AF. To determine whether elderly patients with overlap syndrome have an increased risk of AF. **Methods** In this single center, community-based retrospective cohort analysis, data were collected on 2,873 patients > 65 years of age without AF, presenting in the year 2006. Patients were divided into OSA group (n = 60), COPD group (n = 416), overlap syndrome group (n = 28) and group with no OSA or COPD (n = 2369). The primary endpoint was incidence of new-onset AF over the following two years. Logistic regression was performed to adjust for heart failure (HF), coronary artery disease, hypertension (HTN), cerebrovascular disease, cardiac valve disorders, diabetes mellitus, hyperlipidemia, chronic kidney disease (CKD) and obesity. **Results** The incidence of AF was 10% in COPD group, 6% in OSA group and 21% in overlap syndrome group ($P < 0.05$). After adjusting for age, sex, HF, CKD, and HTN, patients with overlap syndrome demonstrated a significant association with new-onset AF (OR = 3.66, P = 0.007). HF, CKD and HTN were also significantly associated with new-onset AF ($P < 0.05$). **Conclusion** Among elderly patients, the presence of overlap syndrome is associated with a marked increase in risk of new-onset AF as compared to the presence of OSA or COPD alone.

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1 Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the elderly population with approximately 2.2 million people in US and 4.5 million people in Europe having either paroxysmal or persistent AF.[1,2] The median age of AF patients is 75 years with the prevalence of AF in the general population being between 0.4%–1% but increasing to 8% in those over 80 years.[2] Additionally, there has been a 66% increase in hospital admissions for AF in the last two decades due in part to the rapid increase in elderly population.[3,4] The current proven risk factors such as age, hypertension (HTN), heart failure (HF), and obesity do not adequately explain the incidence of AF in the elderly population.

Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) are two of the most prevalent chronic respiratory disorders.[5] The coexistence of OSA and COPD is common and is referred to as the overlap syndrome.[6] Overlap syndrome occurs in 10%–20% of patients with OSA and these patients have greater degree of hypoxemia and hypercapnia than patients with either OSA or COPD alone.[6,7] Overlap patients have greater risk of cardiovascular death.[8] Hypoxia is known to contribute to arrhythmia development and impaired lung function has been shown to be an independent predictor of incident AF.[9–11] Hypoxia and moderately reduced Forced Expiratory Volume in 1 second (FEV1) are associated with incident AF.[10,12]

AF is strongly age-dependent with approximately 70% of the AF patients between 65 and 85 years.[2] Recently, it has been shown that contrary to what has been observed in the general population, elderly patients with only OSA have no

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increased risk of AF.[13] However, the risk of incident AF in elderly population with the overlap syndrome has not been studied. Our primary hypothesis is that elderly patients with the overlap syndrome have higher incidence of AF when compared to elderly patient with OSA alone. This may have implications in identifying the high risk elderly patients for more intensive therapy.

2 Methods

A retrospective cohort analysis was undertaken using data collected from the medical records of Mercy Medical Center, Mason City, IA. Permission was obtained for the use of de-identified data from Mercy Medical Center, North Iowa. Institutional Review Board of Hartford Hospital, Hartford, CT approved the study.

2.1 Patient population

We used the following criteria for this study: (1) subjects between 65 to 89 years; (2) alive throughout the year 2006; (3) admitted to Mercy Medical Center as inpatients in the year 2006; and (4) with subsequent follow-up over the next two years at Mercy Medical Center and its integrated clinics.

AF and atrial flutter patients were identified using ICD 9 codes 427.3, 427.31 and 427.32. Abstracted comorbid conditions included HF, chronic kidney disease (CKD), coronary heart disease (CAD), cerebrovascular accidents (CVA), diabetes, OSA, obesity, HTN, hyperlipidemia, COPD, malignancy, and cardiac valve disorders. We screened 3,867 patients admitted as inpatients to Mercy Medical Center, Mason City in the year 2006. Out of the 3,867 patients, we excluded those patients who died in the year 2006 (n = 121). We characterized patients as deceased if data on death were recorded in the Medicare database. We were unable to identify either a death date or the evidence for follow-up for 16 patients and these individuals were excluded from the analysis. The final study cohort included 3730 patients. The number of patients without AF in the year 2006 was 2873. We divided 2873 patients without AF (n = 2873) into OSA group (n = 60), COPD group (n = 416), OSA plus COPD group (n = 28) and those without OSA or COPD (n = 2369). Figure 1 shows the division of study patients into subgroups. These four groups were followed for two years (January 1st, 2007 to December 31st, 2008) for new-onset AF. We obtained medical records for all subsequent hospitalizations and clinic visits during the follow-up period.

2.2 Identification of OSA and COPD patients

One hundred and seventeen consecutive elderly (≥ 65 years) patients without AF were evaluated in hospital sleep laboratory between January 1st 2006 and December 31st 2006. Chart reviews were done to assess the how these patients were referred for sleep study. Forty-six patients were referred based on clinical assessment and nocturnal oximetry as inpatients. Thirty-four patients were referred after clinical assessment by primary physicians during outpatient follow-up. We could not find the reason for sleep referral in 39 patients. Polysomnographic data were recorded (Somnostar Sleep System, Vyasys Healthcare, CA, USA). During the sleep study, apnea was defined as complete cessation of airflow and hypopnea as more than 50% reduction in airflow for 10 s or more accompanied by a decrease in oxygen saturation of atleast 3%.[14] The apnea/hypopnea index (AHI) was defined as number of episodes of apnea/hypopnea per hour. The diagnosis of OSA was made using established criteria (AHI ≥ 5).[15] Only those patients who had established OSA diagnosis with overnight in-hospital polysomnographic study and on Continuous Positive Airway Pres-

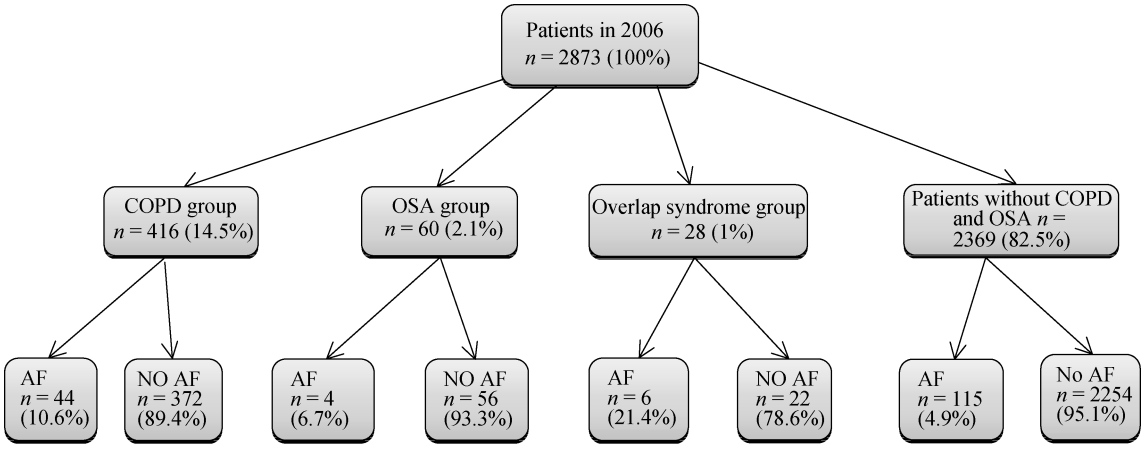

Figure 1. Flowchart depicting the patient groups. AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; OSA: Obstructive sleep apnea.

sure (CPAP) treatment were included in the study (n = 88). Four patients with central sleep apnea/hypopnea were excluded. COPD patients were identified using ICD 9 codes 491, 492, 494, and 496. COPD patients without any evidence of OSA (n = 416) on the sleep study were included in the study. All the COPD patients in our study cohort were on treatment and this was confirmed using subject's home medication list. Figure 1 shows the division of study patients into subgroups. These four groups were followed for two years starting from January 1st, 2007 to December 31st, 2008 for new-onset AF. We obtained medical records for all hospitalizations and clinic visits.

2.3 Identification of AF

Cases of incident AF were identified utilizing two methods: 12-lead electrocardiograms (ECG) and hospital discharge diagnoses. We considered AF to be present at the time of admission if the discharge diagnosis ICD code indicated AF or atrial flutter. Previous studies have shown that the use of hospital records for diagnosing AF has an accuracy of 98.6% and 24-h Holter monitor picked up only 0.1% cases of sustained or intermittent AF not identified by the hospital records.[9,16] The total number of patients with incident AF was 169. Out of the169 patients, 146 had evidence (of AF) from ECG and hospital records, 20 had only ECG evidence and 3 had only hospital records evidence.

2.4 Statistical methods

We compared demographic and clinical variables of patients with and without new-onset AF (Table 1). Comparisons between these groups were made using Chi Square test for the categorical variables and two sample t-test for the continuous variables. Associations were considered significant at P values (two-tailed) below 0.05. Effect of OSA and COPD on the new-onset AF was analyzed after adjusting for clinical variables that were significantly associated with AF. Odds ratio (OR) for new-onset AF was obtained from multiple logistic regression model that included factors that showed association with new-onset AF. We fit the initial models using lasso penalized cross-validation model selection and tested for interactions. We eliminated predictors that were highly correlated. For example, CAD and HF were highly correlated, thus only HF was included in the final model. We used R statistical foundation version 2.14.1 for analysis of the data.

3 Results

3.1 Baseline characteristics

The baseline characteristics of the population with and without new-onset AF (Table 1) show that the mean age of the AF patients was higher than the patients without AF (78.9 ± 7.5 years *vs*. 77.6 ± 7.8 years, respectively, P = 0.029). The prevalence of COPD in those with AF was 26% (44/169) as compared to 14% (372/2704) in those without AF. The prevalence of overlap syndrome in those with AF was 3.5% (6/169) compared to 0.8% (22/2704) in the no AF group. The prevalence of OSA in the new-onset AF group did not differ significantly from those who had no AF (2.4% *vs*. 2% respectively, P = 0.794). Patients with new-onset AF group (n = 169) were older, had greater burden of HF, CKD, CAD, HTN, diabetes, hyperlipidemia and valve disorders when compared to those without AF (P < 0.05).

Table 1. Demographics and clinical characteristics of the patient population which includes the clinical characteristics of new-onset AF patients in comparison to the No-AF group.

Variables	AF (n = 169)	No-AF (n = 2704)	P-Value
Age (yrs, mean ± SD)	78.93 ± 7.5	77.63 ± 7.8	0.029
Overlap Syndrome group	6 (3.5%)	22 (0.8%)	< 0.001
OSA group	4 (2.4%)	56 (2%)	0.794
COPD group	44 (26%)	372 (14%)	< 0.001
Anemia	37 (22%)	454 (17%)	0.087
HF	54 (32%)	370 (14%)	< 0.001
CAD	85 (50%)	950 (35%)	< 0.001
CKD	35 (21%)	237 (9%)	< 0.001
DM	50 (29.5%)	664 (24.5%)	0.142
Obesity	7 (4%)	148 (5.5%)	0.457
Hypertension	119 (70%)	1636 (60.5%)	0.010
Hyperlidemia	70 (41%)	950 (35%)	0.098
CVA	11 (6.5%)	175 (6.5%)	0.985
Valve disorders	27 (16%)	217 (8%)	< 0.001

AF: Atrial fibrillation; CAD: Coronary artery disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular disease; DM: Diabetes mellitus; HF: Heart failure; OSA: Obstructive sleep apnea.

3.2 Effect of overlap syndrome on new-onset AF

During the two year retrospective follow-up, the incidence of new-onset AF was 10.6% in the COPD group compared to 6.7% in the OSA group. Patients with overlap syndrome had 21.4% incidence of new-onset-AF (Figure 2). The incidence of AF in patients without COPD and/or OSA was 4.9%. Since AF could occur as a result of the preceding comorbid conditions, we evaluated the COPD and OSA relationship with new-onset AF after adjusting for HF, CKD, HTN and valve disorders. After applying logistic regression and eliminating the predictors that are highly correlated, we derived the final best fit model which shows that COPD

subgroup (OR: 1.79, 95% CI: 0.190–0.962, $P = 0.003$) and overlap syndrome subgroup (OR: 3.66, 95% CI: 1.056–6.860, $P = 0.007$) have highly significant association with new-onset AF (Table 2). In fact, patients with overlap syndrome demonstrated a two-fold increase in risk of incident AF compared to COPD alone. After adjustment of variables with multiple logistic regression analysis, CKD, HTN, and HF were significantly associated with the new-onset AF (Table 2), however, OSA alone was not predictive of new-onset AF ($P = 0.8799$). Among the comorbid factors, CKD ($P = 0.002$), HF ($P = 0.002$), HTN ($P = 0.001$) were significantly associated with new-onset AF.

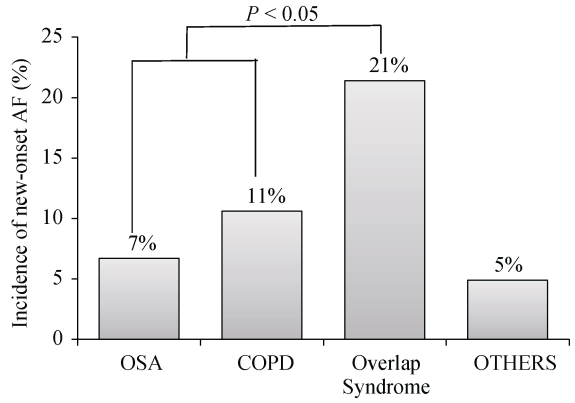

Figure 2. Incidence of new-onset AF in study patients. AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea.

Table 2. Using logistic regression, final model has been derived that is consistent with Chi Square test.

Variables	OR	95% CI	*P* value
Age	1.02	0.001–0.04	0.058
Male	1.81	0.26–0.93	0.001
Overlap syndrome group	3.66	1.06–6.9	0.007
COPD group	1.79	0.19–9.6	0.003
CKD	2.06	0.25–1.19	0.002
HF	1.86	0.22–1.01	0.002
Hypertension	1.94	0.30–1.04	0.001
Valvular disorders	1.55	-0.05–0.89	0.066

Predictors that are highly correlated to each other have been eliminated. For example, CAD and HF are highly correlated, and thus only HF has been included in this model. Final model shows that COPD and COPD plus OSA group is highly significant relationship with new-onset AF. COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease, HF: heart failure; OSA: obstructive sleep apnea.

4 Discussion

The primary finding of our study is that elderly patients with the overlap syndrome (OSA with concomitant COPD) have an increased the risk of new-onset AF when compared to elderly patients with OSA alone. To our knowledge, this is the first study to demonstrate this association in a community-based elderly population**.** Additionally, our study also shows that elderly individuals with the overlap syndrome have a higher risk of new-onset AF when compared to elderly patients with COPD alone.

Although studies have shown that OSA alone does not predict new-onset AF in the elderly,[13] our study demonstrates that overlap syndrome markedly increases the risk of AF in elderly patients. Multiple pathophysiologic factors may contribute to the development of AF in elderly patients with overlap syndrome.

First, previous studies have shown that acute or chronic hypoxia seen in OSA and COPD patients can induce AF by increasing the sympathetic drive.[11,17] Overlap syndrome patients have greater degree of hypoxemia and hypercapnia than OSA-alone patients.[5,18] Overlap syndrome patients have higher incidence of COPD exacerbations and higher mortality.[8] During sleep, patients with overlap syndrome have more frequent episodes of hypoxia, greater amount of total sleep time with hypoxemia and hypercapnea than OSA patients without COPD.[6] Furthermore, during apneic events, overlap syndrome patients have greater degree of hypoxia and higher rate of cardiac arrhythmias.[11] Additionally, the use of sympathomimetic medications (such as bronchodilators) in these patients could worsen sympathetic drive. Excessive sympathetic drive can provoke atrial catecholamine-sensitive ion channels and trigger AF.[13]

Second, systemic inflammation could be a contributing factor to the increased risk of AF in patients with the overlap syndrome. C-reactive protein (CRP) has been shown to be elevated in patients with atrial arrhythmias, particularly persistent AF.[19] OSA patients have been shown to have increased levels of CRP.[20,21] Futhermore, COPD patients have elevated levels of pro-inflammatory cytokines.[22] The common factor for systemic inflammation in OSA and COPD is a response to hypoxia.[23–25] Systemic inflammation can induce atrial structural remodelling and increase the risk for atrial arrhythmias.[19] Third, overlap syndrome patients can develop pulmonary hypertension and pulmonary hypertension is associated with an increased prevalence of AF.[26,27] Patients with overlap syndrome tend to have more severe pulmonary hypertension than those with OSA or COPD alone.[5,6,28] In an study by Hawrylkiewicz and coworkers, 86% of the overlap syndrome patients had pulmonary hypertension as compared to 16% of patients with OSA alone.[29] Thus, the concomitant presence of OSA and COPD has a synergistic effect on pulmonary hemodynamics.

Due to more severe pulmonary hypertension, overlap syndrome patients could have greater degree of right ventricular (RV) dysfunction. This is supported by a recent small pilot study showed that overlap syndrome is associated with increased RV mass and RV remodelling compared to COPD alone.[30]

Fourth, OSA patients are characterized by high negative intrathoracic pressure against an occluded upper airway.[31] This severe negative intrathoracic pressure causes sudden decrease in left atrial (LA) volume and LV systolic performance, leading to an increase in LV transmural pressures. Such sudden, repeated alterations in afterload pressures and chamber volumes can have a synergistic effect on increasing the risk of AF.[32] Additionally, recent evidence points to the fact that OSA is independently associated with increased arterial stiffness.[33] The increased arterial stiffness leads to an increased LV afterload which causes enlargement of the LA diameter and thus an increased propensity for AF.[33] COPD in the form of emphysema has also been associated with a higher degree of arterial stiffness.[34] Thus, patients with overlap syndrome are more likely to have an increased LA diameter and thus a higher risk for AF.

The amplification of the above discussed pathophysiologic processes in the presence of OSA and concomitant COPD may have contributed to the increase atrial arrhythmogenesis in our study patients with overlap syndrome as compared to those with OSA or COPD alone.

4.1 Limitations

Our study is retrospective in design and, therefore, subject to the inherent limitations of such a design. Our findings are confined by design to community-based elderly population and, therefore, may not be generalizable to a broader patient population but that was not the intent of the study. The relatively small number of patients with OSA and COPD as well as those with OSA alone may be a limitation, although the large study cohort, gives excellent power. Even though we employed strict parameters for diagnosing new-onset AF, asymptomatic cases of paroxysmal AF could have been missed and the incidence of AF may even be underestimated due to the short follow-up period of two years. Despite strict inclusion criteria, it is still possible that we could have underestimated the number of OSA patients since OSA is frequently under-diagnosed in the elderly population.[35] Our study findings are also limited by the fact that subjects in non-OSA group were not evaluated with a sleep study. Our data are centered on those elderly patients with a COPD diagnosis by ICD 9 codes and does not include data on FEV1 or smoking status of the subjects. Data on adherence and efficacy of treatment for OSA and COPD in our study patients are also not available and the study design does not provide conclusions on causality. Our objective was not to find the mechanisms behind the increased risk of AF in this elderly subgroup; therefore, further studies are needed to better define the etiology behind the increased risk.

4.2 Conclusions

In this large, community-based cohort of elderly patients, the presence of overlap syndrome is associated with a significantly higher risk of new-onset AF when compared to patients with OSA alone. Our results have significant implications in the identification of new risk factors for the AF epidemic in a population that is at highest risk for AF. The interaction between OSA and COPD and its role in pathophysiology of AF needs to be further studied in large randomized trials. This finding may enable clinicians to identify the subgroups of elderly patients who might benefit from a focused treatment to prevent incident AF. Additionally, routine electrocardiogram monitoring may be helpful in this subgroup of the elderly population to aid in the identification of new-onset AF.

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