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Polysomnography in AF patients without prior diagnosis of obstructive sleep apnea reveals significant sleep abnormality: A strong case for screening in all patients with atrial fibrillation?



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ABSTRACT

Background: Obstructive sleep apnea (OSA) and atrial fibrillation (AF) are known to often coexist together. However, whether all patients with AF should be screened for sleep abnormalities is not clear. No previous study has examined the association of asymptomatic OSA with AF.

Objective: This study sought to determine the prevalence of asymptomatic OSA in patients with persistent AF and whether asymptomatic OSA is an independent risk factor for atrial fibrillation.

Method: Patients with persistent AF without a prior diagnosis of OSA and asymptomatic for sleep abnormalities were prospectively enrolled over 12 months. All patients underwent polysomnography after informed consent. Patients without AF or OSA who underwent polysomnography during the same period served as controls.

Results: A total of 97 patients were studied; 50 were in the case group (patients with persistent AF) and 47 were in the control group (patients in sinus rhythm). Asymptomatic OSA was diagnosed on polysomnography in 72% of patients in the AF group and 17% of the control population. Multivariable analysis of factors including diabetes, hypertension, coronary artery disease, hypothyroidism, prior MI, and asymptomatic OSA, suggested asymptomatic OSA as an independent factor associated with AF.

Conclusion: A significant proportion (72%) of patients with persistent AF have underlying asymptomatic OSA. Sleep abnormality thus has a strong association with AF even in patients who are asymptomatic for OSA. Screening for OSA may be advised for all patients with AF, as this may have significant implications for management.

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1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias, leading to increased mortality, morbidity, and frequent hospital admissions. The prevalence of non-valvular AF in the general population increases with age [1]. Significant number of AF patients have associated extra-cardiac risk factors, including hypertension, diabetes, and obesity [2].

Obstructive sleep apnea (OSA) is the most common sleep-breathing disorder (SBD). It is characterized by repetitive airway obstruction of the upper airway leading to recurrent hypopneas (reduction in airflow of >50%) or apneas (cessation of airflow for

more than >10 s). These episodes are often associated with oxy-hemoglobin desaturation followed by cortical arousal, leading to sleep fragmentation [3]. Diagnosis and evaluation of OSA start with a comprehensive sleep assessment that includes a detailed clinical history, documenting signs and symptoms like excessive daytime sleepiness, morning headaches, snoring, documented apnea, or difficulty in concentrating. Physical examination and a review of the medical history for relevant co-morbidities and other risk factors are also important in the evaluation of OSA. Diagnosis is usually made when a patient has an apnea-hypopnea index (AHI) ≥ 5 on polysomnography [4].

The relationship between OSA and AF is complex. The two diseases are linked to each other at the neuro-humoral and cellular levels. Obstructive sleep disorder and AF share many common risk factors [5]. The pathophysiologic mechanisms of the association between AF and OSA are multifactorial. One widely recognized theory is that repeated forced inspiration against closed airways

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results in negative intra-thoracic pressure, which increases cardiac afterload, increases atrial wall stress, and therefore predisposes to arrhythmia [6].

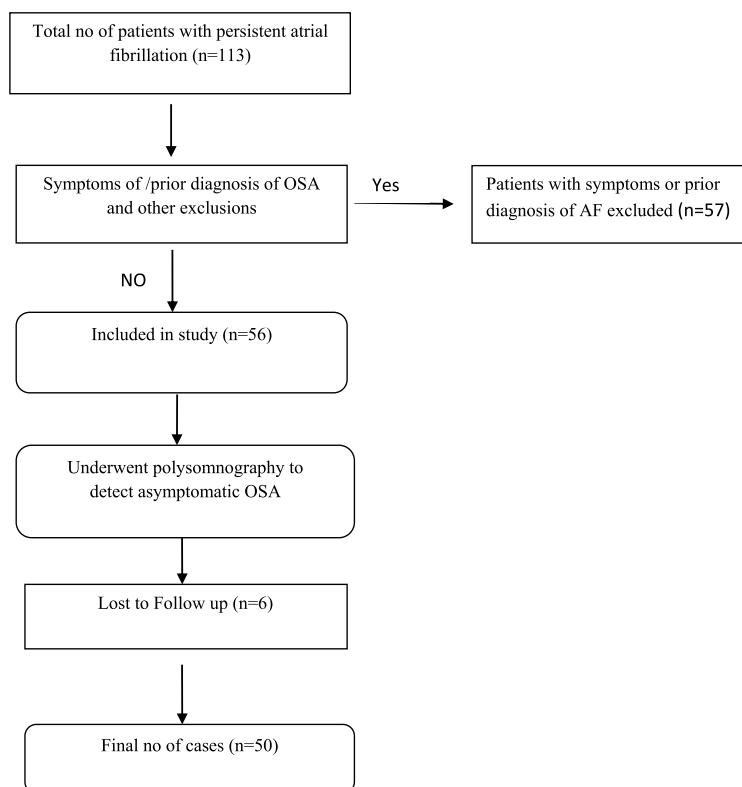
Although co-existence between OSA and AF has been previously noted, the prevalence of asymptomatic OSA (patients without any symptoms related to OSA) in AF patients has not been systematically assessed.

Polysomnography is the gold standard for the diagnosis of OSA [7]. We conducted a prospective study to determine the prevalence of OSA in patients with persistent AF without previously diagnosed OSA and asymptomatic of any sleep abnormality to determine if the two are associated.

2. Methods

A single-center prospective case-control study was done in our hospital from 1 April 2020 to 31 March 2021. All patients with non-valvular persistent AF presenting during this period, who did not have a previous diagnosis or symptoms suggestive of OSA (like snoring, excessive daytime sleepiness, excessive daytime fatigue, difficulty in concentration) were enrolled (case group). Screening for OSA was done using a predefined and validated questionnaire [8]. These patients underwent polysomnography to diagnose asymptomatic OSA. Patients who came to our outpatient department without any previous diagnosis of OSA or AF and who underwent polysomnography during the same period served as controls (Tables 1 and 2). Informed consent was given by all patients. The study was approved by the institutional ethics committee.

Table 1
Flow diagram showing the inclusion of cases.



2.1. Exclusion criteria

Patients with the following conditions were excluded:

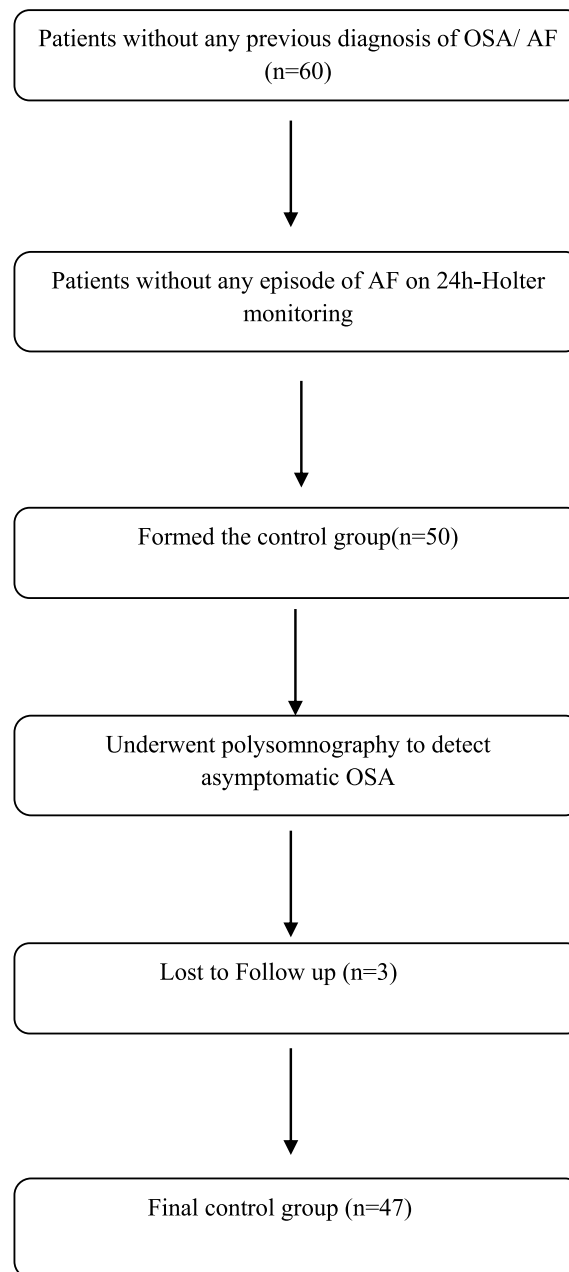
- AF patients with a previous diagnosis or history suggestive of OSA
- Valvular AF
- AF in intensive care unit settings
- Post-op AF
- Pericardial Disease
- Alcohol and/or drug abuse
- Pregnancy
- Patients on dialysis

Persistent AF was defined as continuous AF that lasts longer than 7 days [9]. The prevalence of sleep-disordered breathing was determined using polysomnography (Sleep Fairy PSG BAMC PSG machine). Sleep studies were analyzed and scored independently by two experienced polysomnographic technologists. The apnea-hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of sleep. We prospectively defined OSA as an AHI score of 5 [3].

2.2. Statistical analysis

Data analysis was performed using GraphPad Prism version 9. All descriptive variables are quantified as mean ± SEM (standard error of the mean). The test for difference in means was done using an unpaired *t*-test with or without Welch's corrections for unequal variances or equal variances, respectively. Fisher's exact test was

Table 2
Flow diagram showing the inclusion of controls.



used to test for differences in the proportions of variables measured. Multiple linear regression analysis was done to evaluate the influence of other factors (diabetes mellitus, hypertension, prior myocardial infarction, clinical hypothyroidism, and coronary artery disease) on AF, in addition to OSA. The level of significance was estimated at $\alpha = 5\%$ or P-value < 0.05 .

3. Results

Demographic characteristics of both cases and the control group are shown in Table 3. The two groups were matched for age and gender. There was no statistical difference in body mass index (BMI) between the two groups (Fig. 2). Clinical hypothyroidism, chronic lung disease (both obstructive and restrictive), prior MI,

cardiomyopathy, diabetes mellitus, hypertension, congestive cardiac failure, and coronary artery disease were more prevalent in the AF group. The left ventricular ejection fraction (mean \pm SD) was 52 ± 7.62 in the case group and 54.4 ± 3.64 in controls ($p 0.053$).

3.1. Sleep apnea and atrial fibrillation

AHI value ≥ 5 is a quantitative index for sleep apnea. To measure the effect of sleep apnea on AF, the two groups were compared for the difference in the mean value of AHI and the difference in proportions of individuals with sleep apnea (AHI ≥ 5). The mean AHI was 4.404 ± 5.609 in the control group compared to 11.26 ± 7.491 in the case group ($P < 0.0001$). The proportion of individuals with sleep apnea in the AF group was considerably higher (72%), as

Table 3
Demographic characteristics of study populations.

	Control (n)	Case (n)	p-value
Age (Years)	62.13	63.72	0.542
BMI	25	26.25	0.187
Gender			
Male	31	33	
Female	16	17	
Male: Female	1.94	1.94	P > 0.99
Congestive Cardiac Failure (CCF)	0	2	P < 0.05
Clinical Thyroid Disease	6	12	P < 0.05
Chronic Lung Disease	2	0	P < 0.05
Prior Myocardial Infarction (MI)	3	11	P < 0.05
Cardiomyopathy	1	7	P < 0.05
Diabetes Mellitus (DM)	11	22	P < 0.05
Systemic Hypertension (HTN)	8	28	P < 0.05
Coronary Artery Disease (CAD)	4	14	P < 0.05

compared to the control group (17%) ($p < 0.0001$). (Fig. 1A and B, Tables 4A and 4B).

3.2. Statistical analysis of the contribution of co-morbid parameters

A multivariable analysis was performed to estimate the role of parameters other than sleep apnea as a contributing factor to AF. Hypertension, DM, prior MI, CAD, and OSA were independently associated with AF (Fig. 3), whereas thyroid disease and cardiomyopathy were not independently associated with AF. The association of OSA with AF was strongest, and the association was independent of other variables. Within the group of patients with

AF, a subgroup analysis (between patients with $AHI \geq 5$ and with $AHI < 5$) of parameters, namely, diabetes mellitus, hypertension, prior myocardial infarction, clinical hypothyroidism, and coronary artery disease (which were statistically different between cases and controls), was done. These risk factors did not seem to have any significant effect on the association between AF and OSA (Fig. 4).

4. Discussion

This study demonstrates a high prevalence of asymptomatic OSA in the AF population. More than 2/3rd (72%) of AF patients has asymptomatic OSA, compared with a significantly lower prevalence in the age and gender-matched control population. Such a large magnitude of association may not be replicable with a larger study population. These findings suggest a causative link between OSA and AF, which was independent of other cardiovascular risk factors. In our study, both cases and controls had comparable BMI, and the prevalence of obesity was not significantly different between the two groups. Multivariable analysis indicates that asymptomatic sleep apnea could be an independent predictor for the development of AF (Fig. 4).

Despite the increasing incidence of OSA in both AF and obesity, there is insufficient evidence for screening for OSA in an asymptomatic population. Many studies have investigated the prevalence of symptomatic OSA in patients with AF. To our knowledge, none of the studies has investigated the prevalence of asymptomatic OSA in patients with AF [10–12]. Gami et al. observed a significantly higher prevalence of sleep apnea in 151 patients with AF referred for cardioversion (49%) than in a control population of 373 patients

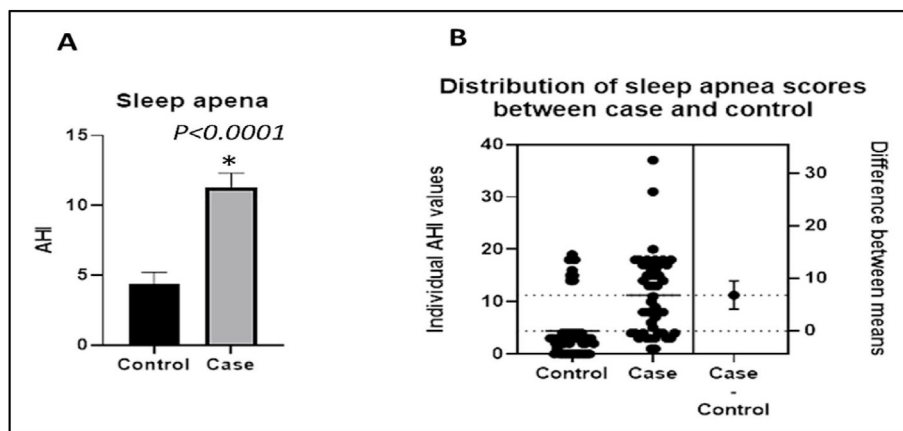


Fig. 1. Association of sleep apnea ($AHI \geq 5$) with AF.

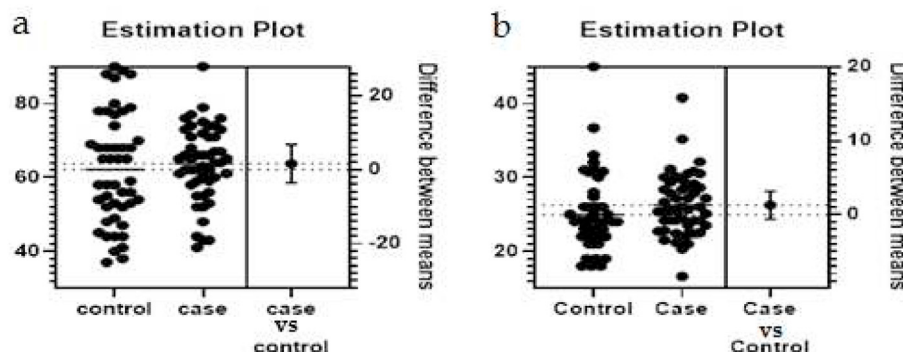


Fig. 2. Age (A) and BMI (B) distributions in the control and case (patients with AF) groups.

Table 4

Table 4A and 4B shows descriptive statistics for AHI values in the control (without AF) and case (with AF) groups.

Table 4A			
Population	Control	Case	Total
AHI (≥5)	8 (17%)	36 (72%)	44
AHI (<5)	39 (83%)	14 (28%)	53
Total	47	50	97

Table 4B			
	Control	Case	
Number of subjects	47	50	
Minimum AHI	0	1	
Maximum AHI	19	37	
Mean AHI	4.404	11.26	
Standard deviation	5.609	7.491	
Standard error of the mean	0.8182	1.059	

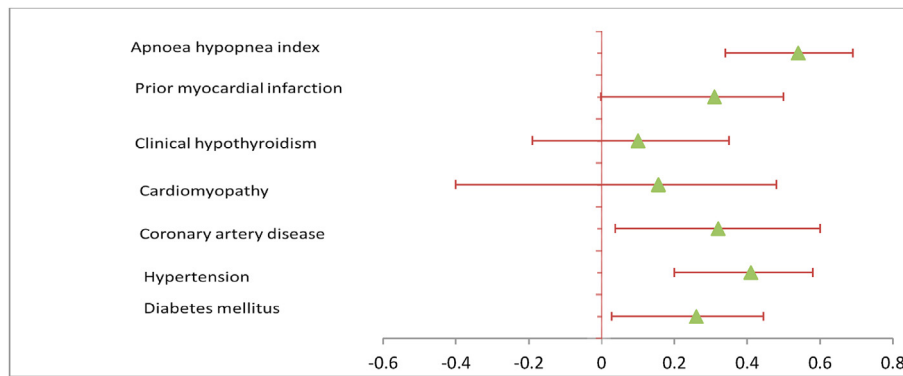


Fig. 3. Forest plot showing an independent association of risk factors with AF.

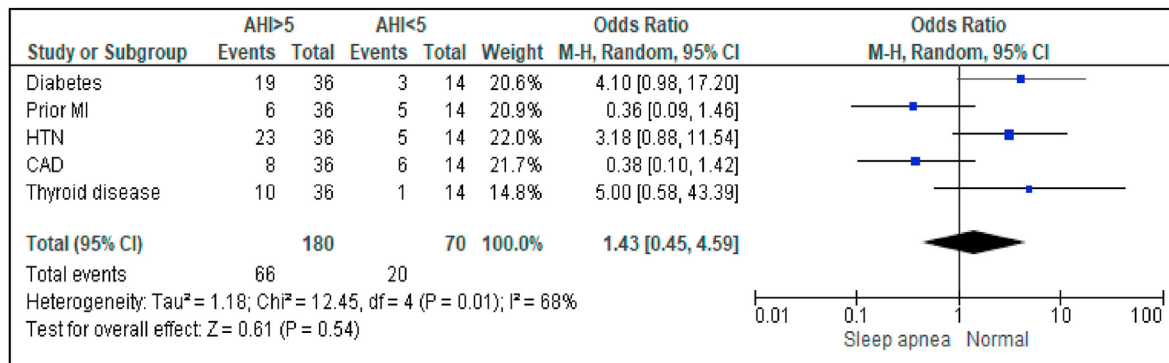


Fig. 4. Multivariable Analysis Showing no Confounding Influence between the listed co-morbidities and the association of sleep apnea and AF.

(32%). The investigators used the Berlin Questionnaire to diagnose sleep apnea [11]. They found that approximately half of their patients with AF were likely to have OSA, and the association of OSA with AF was greater than the association of OSA with traditional OSA risk factors such as body mass index, neck circumference, and hypertension. Similar to our study, established cardiovascular diseases, such as coronary artery disease and congestive heart failure, were more prevalent in patients with OSA. Stevenson et al. enrolled 99 patients with paroxysmal or persistent AF and 45 controls. All patients had normal LV function. SBD was diagnosed using all-night portable polysomnography. The proportion of patients with significant SBD (AHI ≥ 15) was greater in AF patients (62% vs. 38%, P < 0.01) [12].

Our study did not reveal any significant difference in BMI between the two groups. This finding can be explained as we had already excluded patients with AF with a prior diagnosis of OSA, who are more likely to have a higher BMI. The mean BMI of our population was 26.6 compared to previous studies that had a higher mean BMI of 27.9 in the AF population [12]. There was no independent association of thyroid diseases with AF. The only thyroid disorder present in some of our case (n = 6) and control (n = 12) patients was clinical hypothyroidism. None of them had hyperthyroidism. An association between AF and hypothyroidism has never been documented [13].

We did not find any independent association of cardiomyopathy with AF. In our study, four patients with cardiomyopathy had HCM.

The lack of any significant association between cardiomyopathy and AF may be because of the small sample size.

4.1. Clinical implications

Our results are consistent with previous studies showing a higher prevalence of OSA in the AF population. This study was unique in that patients with a previous diagnosis of OSA or symptomatic sleep abnormality were excluded, and we found the prevalence of asymptomatic OSA to be higher in the AF group. Diagnosing OSA at an early stage and implementing appropriate intervention may improve outcomes in AF patients.

4.2. Limitation

Small sample size was one of the major limitations of this study. In this preliminary study, we tried to explicate the association between asymptomatic OSA and atrial fibrillation. Further studies with a larger sample size are warranted to answer these questions.

5. Conclusion

In our study, asymptomatic OSA was prevalent in 72% of the patients with persistent AF; this was significantly higher than in the control group (17%). Sleep abnormality thus has a strong association with AF even in patients who are asymptomatic for OSA. Screening for OSA may be advised for all-comer AF patients, as this may have significant implications for management. But these findings need to be confirmed in larger trials.

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Declaration of competing interest

None for all authors.

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