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Atrial fibrillation is associated with central sleep apnea in clinic patients undergoing diagnostic polysomnography

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Abstract

Introduction: Sleep apnea is highly prevalent in patients with atrial fibrillation (AF). Obstructive sleep apnea (OSA) is the most common type, and best studied in the context of AF. However, recent investigations have indicated that central sleep apnea (CSA) may be a risk factor for incident AF. We evaluated the burden of CSA events in patients referred for diagnostic polysomnography (PSG) and whether AF is associated with CSA.

Methods: We identified patients with and without a history of AF who underwent clinically indicated PSG in a matched manner. OSA was defined as obstructive apnea-hypopnea index (AHI) ≥15/h, and CSA was defined as central apnea index (CAI) ≥5/h. The association between AF and CSA was evaluated using multivariable logistic regression.

Results: Among 465 patients included, mean AHI was 25.5/h, and mean CAI was 1.7/h. OSA prevalence was 53.3%, while CSA prevalence was 8.4%. The prevalence of OSA in the AF and non-AF groups (54.7% vs 52.0%, $P = .56$) was similar. CSA was more common in the AF group (12.3% vs 4.4%, $P = .002$). In multivariable analysis, AF (OR: 2.19 [1.02, 5.03], $P = .05$), male gender (OR: 2.5 [1.17, 5.84], $P = .02$), and older age (OR: 2.44, [1.16, 5.46], $P = .02$) were associated with CSA.

Conclusion: Though CSA is much less common than OSA in patients with AF, the presence of AF is independently associated with CSA.

KEYWORDS

atrial fibrillation, central sleep apnea

1 | INTRODUCTION

Atrial fibrillation (AF) is the most commonly diagnosed chronic arrhythmia and its prevalence is expected to rise as the population ages.[1] Sleep apnea is an extremely common condition which can impair sleep quality and daytime wakefulness, and appears to play a role in the pathogenesis of AF.[2,3] For example, it is known that sleep apnea is associated with a higher prevalence of AF[4] as well

as a higher burden of nocturnal AF.[5] A causal link is supported by observational studies which show that sleep apnea is associated with increased recurrence of AF following both cardioversion and catheter ablation, the latter potentially dependent upon the ablation technique employed.[6-8] Furthermore, AF ablation candidates demonstrate a high burden of undiagnosed sleep apnea.[9]

While the term "sleep apnea" is frequently used synonymously with obstructive sleep apnea (OSA) in the common and medical literature, there is an increasing focus on the other subtype, central sleep apnea (CSA), in examining the association of sleep apnea with cardiovascular conditions. The clinical differentiation of OSA and CSA is typically based on the dominant type manifested during polysomnography (PSG).[10] Unlike obstructive apneas, central apneas are characterized by the absence of adequate respiratory effort. CSA is uncommon, and found mostly in patients with congestive heart failure (CHF), acute stroke, or on chronic opioid therapy.[10] CSA is also commonly observed at high altitude, and is sometimes elicited in patients with OSA who are initiated on continuous positive airway pressure (CPAP) therapy.[10,11]

However, it is important to recognize that central apneas or hypopneas (in contrast to the diagnosis of CSA) are not infrequently observed during sleep. For example, central apneas are commonly seen during sleep-wake transition or immediately following arousal, and are at times present even in the setting of OSA due to high loop gain.[11,12] This is commonly evidenced by the emergence of CSA following management of OSA with CPAP therapy.[11,13]

Although a majority of studies have focused on OSA and its association with AF, recent investigations have signaled a potential link between CSA and AF. In two recent cohort studies, which included community dwelling adults without known CHF, the presence of CSA predicted incident AF.[14,15] In contrast, no such association was seen with measures of OSA. These findings highlight the complex relationship between sleep apnea and AF. We seek to evaluate this association by assessing the burden of CSA in patients with AF.

2 | METHODS

2.1 | Study design and participants

We reviewed the records of patients referred for laboratory-based diagnostic PSG at the University of Virginia Sleep Laboratory between January 2010 and December 2019. All PSGs were scored by a registered PSG technologist and then reviewed by board-certified sleep physicians. We first constructed a case cohort consisting of patients with prior history of AF and then constructed a control cohort of equal number by including consecutive patients without prior history of AF between June and December 2019. Only patients with a total sleep time (TST) >4 hours were included.[16,17]

The diagnosis of AF was confirmed via independent chart review by two authors who were blinded to PSG results. We only included patients whose AF diagnosis preceded the timing of their diagnostic PSG. AF was classified as either paroxysmal or persistent/permanent. Patients already on CPAP therapy were excluded. Separately, among those with a history of AF, "nocturnal AF" was ascertained if AF was detected during diagnostic PSG. This study was approved by the institutional review board at the University of Virginia.

2.2 | Sleep study

The standard channels recommended by the American Academy of Sleep Medicine (AASM) were used to perform overnight PSG, and data were processed with Embla Sandman Elite software (Natus Medical Incorporated). Split night and PAP titration studies were excluded. Apnea-hypopnea index (AHI) was defined as the number of apnea and hypopnea events divided by TST, expressed as events per hour. Apnea was defined as a reduction in airflow greater than 90% of the pre-event baseline and occurring for ≥10 seconds measured using a thermocouple signal, while hypopnea events were defined as a reduction in airflow >30% of the pre-event baseline and occurring for ≥10 seconds in association with either at least a 3% oxygen desaturation or arousal.[18] Hypopnea was considered obstructive in nature if any of the following were present: snoring during the event, an increase in the flattening of the nasal pressure flow, or paradoxical breathing. Obstructive AHI ≥ 15 events/hr was considered clinically significant for OSA.

Central apneas were defined as apneas occurring in the absence of associated respiratory effort lasting ≥10 seconds. Post-arousal CSA or CSA that occurs in sleep-wake transitions was included as long as it met the criteria. The central apnea index (CAI) was calculated by dividing the total number of central apnea events by the TST. For the purpose of this study, CSA was defined as CAI ≥ 5 events per hour regardless of the dominant subtype of sleep apnea. Given that many patients exhibit both obstructive and central apneas throughout a single PSG, we also classified CSA-dominant (CSAd), which was defined as >50% of total apneic events being central, and "true CSA" (by conventional criteria), defined as CSAd that also meets CAI ≥ 5.[18] Therefore, it was possible that a single patient could exhibit an OSA-dominant (OSAd) phenotype overall but could still have coexisting CSA.

2.3 | Covariates

Covariates of interest included age, gender, body mass index (BMI), and a medical history significant for hypertension and/or CHF. Age was classified into older and younger cohorts by median age. Obesity was defined as BMI >30 kg/m^2. With regard to CHF, patients with both systolic and diastolic dysfunction were included. We initially screened our cohort by identifying any patient with an ICD-10 diagnosis of CHF. Of the patients identified, we then confirmed the presence of clinically relevant CHF by individual chart review. In addition, we reviewed available cardiac imaging results of all the included patients. Any patients with an ejection fraction (EF) of <40% within 1 year from PSG were considered to have CHF. Of those with EF ≥ 40%, patients were considered to have clinically relevant CHF if one or both of the

following were present: (a) EF formerly reduced to <40% which had since recovered, or (b) any hospitalization for HF exacerbation.

2.4 | Statistical analysis

For categorical variables, either Chi-square or Fischer's exact test was used as appropriate. Mann-Whitney test was used to compare sleep apnea measures between patients with and without AF. A multivariate logistic regression model was used to examine the independent association between AF and CSA adjusting for age, sex, obesity, hypertension, and CHF. Because of the rarity of true CSA cases, and the consequent limitation of the logistic model, multivariable analysis was not performed for this outcome. Values were expressed as mean (SD) unless otherwise specified. For all analyses, a two-tailed $P < .05$ was considered significant. All analyses were performed using SAS software v. 9.2 (SAS Institute Inc.).

3 | RESULTS

A total of 465 patients undergoing diagnostic PSG were included. The majority of the cohort was male (57%) with a median age of 66 years and mean BMI of 32.3 kg/m^2. By study design, half of the included patients (236) had AF (50.8%). Of the AF patients, 182 (77.1%) had paroxysmal AF, while 54 (22.9%) had either persistent or permanent AF. With regard to procedural interventions, 86 AF patients (36.4%) had undergone catheter ablation, and 86 (36.4%) had undergone cardioversion. The mean CHADS2 score[19] of patients with AF was 2.02 (SD ± 1.29). In this cohort of 465 patients, the overall prevalence of OSA and CSA were 53.3% and 8.4%, respectively. The mean AHI was 25.5 events/h, while the mean CAI was 1.66 events/h (Table 1).

When comparing patients with and without AF, those with AF were older, more likely to be hypertensive, and were more likely to have CHF (Table 1). There was no difference in OSA prevalence (54.7% in patients with AF, and 52.0% in patients without AF, $P = .56$). However, patients with AF were found to have a significantly higher prevalence of CSA compared to those without (12.3% vs 4.4%, $P = .002$, Figure 1). The prevalence of CSA was similar between paroxysmal versus persistent/permanent subtypes (12.6% vs 11.1%, $P = .764$). Of patients with AF, 34 (27%) were noted to have nocturnal AF (AF manifested during PSG). The prevalence of CSA was similar between AF patients who exhibited nocturnal AF and those who did not (1/34 vs 14/202, $P = .778$). CSAd and true CSA were rare overall (17/465 patients, 3.7% and 11/465 patients,

TABLE 1 Demographic comparisons and sleep indices

	Atrial fibrillation (n = 236)	Control (n = 229)	*P*-values
Sex	M = 143 (60.6%)	M = 121 (52.8%)	.111
	F = 93 (39.4%)	F = 108 (47.2%)	
Age (mean ± SD)	66 ± 11.8	60 ± 13.9	<.001**
Age ≥ 66	141 (59.7%)	92 (40.2%)	<0.001**
Age < 66	95 (40.3%)	137 (59.8%)	<.001**
BMI (mean ± SD)	32.2 ± 7.8	32.3 ± 8.5	.895
Hypertension	123 (52.1%)	155 (67.7%)	<.001**
Congestive heart failure	43 (18.2%)	13 (5.7%)	<.001**
Ejection fraction (mean ± SD, %)	49.9 ± 13.7	54.2 ± 10.2	<.001**
Coronary artery disease	74 (31.3%)	45 (19.7%)	.004**
Diabetes mellitus	100 (42.4%)	79 (34.5%)	.081
Stroke/TIA	21 (8.9%)	8 (3.5%)	.02*
Epworth sleepiness scale (mean ± SD)	9.84 ± 5.0	9.94 ± 5.5	.850
Obstructive sleep apnea	129 (54.7%)	119 (52.0%)	.560
CSA	29 (12.3%)	10 (4.4%)	.002**
CSA dominant	15 (6.4%)	2 (0.87%)	.002**
True CSA	9 (3.8%)	2 (0.87%)	.037*
CAI (mean ± SD, events/h)	2.41 ± 7.0	0.880 ± 3.13	.003**
AI (mean ± SD, events/h)	29.7 ± 25.4	30.4 ± 27.7	.777
AHI (mean ± SD, events/h)	26.6 ± 24.0	24.2 ± 24.6	.288
OAI (mean ± SD, events/h)	15.3 ± 19.0	20.7 ± 22.3	.065

Abbreviations: AHI, apnea-hypopnea index; AI, arousal index; BMI, body mass index; CAI, central apnea index; CSA, central sleep apnea; OAI, obstructive apnea index; SD, standard deviation.

*$P < .05$;

**$P < .01$.

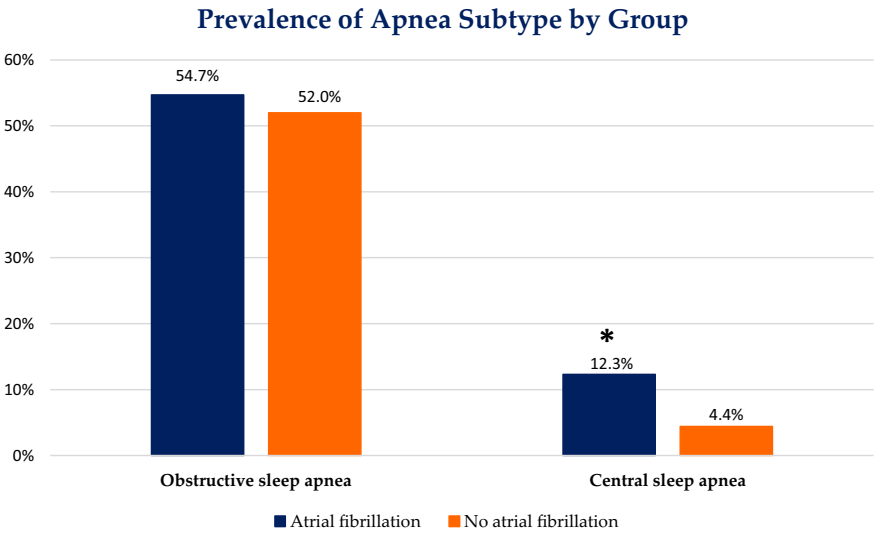

FIGURE 1 Comparison of apnea subtype prevalence between patients with and without AF. No difference in prevalence of obstructive sleep apnea was observed between the two groups, while there was a significantly higher prevalence of central sleep apnea in patients with AF [Colour figure can be viewed at wileyonlinelibrary.com]

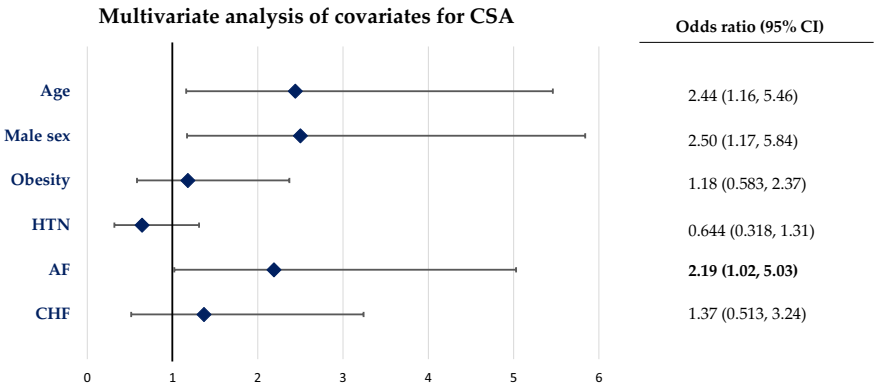

FIGURE 2 Multivariate logistic regression analysis of covariates. Only age category, male sex, and AF were found to predict CSA. CSA, central sleep apnea; HTN, hypertension; AF, atrial fibrillation; CHF, congestive heart failure; OR, odds ratio; CI, confidence interval [Colour figure can be viewed at wileyonlinelibrary.com]

2.4%). However, the prevalence of both CSAd and true CSA was significantly higher in patients with AF (vs without AF; Table 1).

Multivariable logistic regression analysis demonstrated that AF was predictive of CSA (OR: 2.19 [1.02, 5.03], $P = .05$) but not OSA (OR: 1.21 [0.80, 1.82], $P = .373$). Male gender and age were associated with CSA (OR: 2.5 [1.17, 5.84], $P = .02$; OR: 2.44, [1.16, 5.46], $P = .02$, respectively). Obesity, hypertension, and CHF were not associated with CSA (Figure 2).

4 | DISCUSSION

We found that both significant CSA as defined in this study (CAI > 5/h) and true CSA by conventional criteria (CAI ≥ 5/h and >50% CSA) were uncommon in patients with AF, with the prevalence of 12.3% and 2.4%, respectively. However, despite the low prevalence, there was a significant association between AF and CSA. To our knowledge, this study represents the first in-depth study to examine the prevalence of CSA in patients with AF from a sleep-lab referred population.

Historically, the relationship between sleep apnea and AF has primarily focused on OSA. However, delineation of the link between OSA and AF is challenging due to the multiple shared risk factors between the two entities, including older age, male sex, hypertension, CHF, and coronary artery disease.[15] Emerging evidence suggests that CSA may also play an important role in AF pathogenesis even in patients without comorbidities that are often associated with CSA, such as opioid-dependence, CHF, or acute stroke.[14,20] Our results suggest an association between AF and CSA, as the prevalence of CSA was significantly higher in patients with AF than in those without. Interestingly, the prevalence of OSA did not differ between the two groups. Recent large community-based studies have demonstrated similar findings. For example, in a cohort of 843 ambulatory older men, CSA was predictive of increased AF risk.[15] Additionally, subgroup analysis of the Sleep Heart Health Study, which included over 2000 patients, demonstrated that CSA, not OSA, was associated with incident AF.[15] Our study is comparable to these studies in that CSA was similarly defined and that the majority of patients with CSA also had significant OSA.

Notably, in addition to AF, we also found male sex and older age to be associated with an increased risk of CSA, which is consistent with findings from prior studies.[21,22] In our cohort, we found that the vast majority of CSAd patients also had AF (88%). This would suggest that the association between CSA and AF becomes even more pronounced in those patients with a relatively high number of central apneic events during diagnostic PSG. Such

a proposition may be supported by a prior study[23] that showed markedly higher prevalence of AF in patients with idiopathic CSA without CHF (27%) as compared with those with OSA (1.7%) or no sleep apnea (3.3%).

Interestingly, there was no association between CHF and CSA, despite their well-documented relationship in the literature. The high prevalence of CSA in patients with CHF is well-recognized,[24] and elevated CAI has been associated with AF prevalence in CHF patients.[25] In our study, however, only 8% of those with CHF had CSA overall, and even fewer patients (3% of CHF) exhibited CSAd. The absence of association between CSA and CHF could be attributed to lack of power given the small number of CSA cases, but it is also important to note the subtle differences in definitions of CSA used in various studies, particularly those involving CHF patients. Even so, the prevalence of CSAd, which is how most other studies have defined CSA in examining its prevalence in CHF cohorts, was much lower in our cohort compared to prior investigations.[26,27] Given that the majority of patients had significant OSA, it is possible that central respiratory events may have been underestimated, possibly owing to under-appreciation of central hypopnea.[28] However, given a comparable prevalence of true CSA in the control group of our study (2.4%) to that reported from a community-based cohort,[29] systematic underscoring of CSA seems less likely. Differentiation of central versus obstructive hypopnea is known to be extremely challenging and highly variable in practice.[18,28]

In this regard, it is important to recognize that differentiation of subtypes of sleep apnea for a given respiratory event is often unreliable using standard PSG without means of measuring intrathoracic pressure.[10,30] Moreover, it is equally important to understand the real existence of pathophysiological overlap across the spectrum of OSA and CSA phenotypes.[31,32] Another challenge is that though many patients in the clinical setting demonstrate both OSA and CSA events, studies often only report the dominant sleep disorder phenotype, classically defined as the type of sleep apnea comprising >50% of total nocturnal events.[10] This is illustrated by the interesting phenomenon of OSAd patients converting to CSAd once on CPAP therapy.[33]

Unlike in CHF, where multiple mechanisms including upregulated loop gain and compromised cerebrovascular response to transient hyper- and hypocapnia are implicated, the mechanisms linking CSA and AF are unclear. Although many patients with AF do not necessarily have overt CHF, many may have underlying diastolic dysfunction, which may trigger CSA in a fashion similar to that of CHF with reduced EF.[34] It is possible that high loop gain, the probable underlying cause of many CSA events, may be a marker of autonomic dysfunction frequently present in patients with AF.[35]

An important observation in this study is that despite this interesting potential relationship between CSA and AF, CSA itself remains an extremely rare clinical entity as a whole. OSA is a much more common phenotype than CSA in patients with AF. Thus, it will be critical to develop a more refined understanding of what impact, if any, CSA has on clinical outcomes in patients with both AF and OSA. In addition, how such a relationship might be affected by CPAP therapy would be worthy of investigation.

As with all retrospective investigations, our study is limited by selection bias given that only referred patients were included. However, both cases and controls were subject to the same bias. The fact that our study cohort was comprised of patients referred to a sleep center may explain such high prevalence of OSA in both groups. This study is also unable to demonstrate any causal relationship between CSA and AF, despite finding an association between the two. Additionally, though we did exclude patients on CPAP therapy, we did not include information regarding opiate medication use, which can increase the likelihood of CSA. Finally, due to the small number of true CSA cases in our cohort, multivariable analysis was not feasible. However, our study findings suggest that the quantity of CSA events (rather than dominance) is important in the association between AF and CSA, which is supported by recent prospective studies.[14,15]

5 | CONCLUSION

Though CSA is much less common than OSA in patients with AF, the presence of AF is independently associated with CSA. Clinical underpinning of the association warrants further investigation.

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CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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