Prevalence and predictors of Sleep Apnea in Atrial Fibrillation patients

Apnées du sommeil chez les patients en Fibrillation Auriculaire : Prévalence et facteurs prédictifs

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RÉSUMÉ

Introduction : Le syndrome d'apnées hypopnées obstructives du sommeil (SAHOS) constitue un réel problème de santé publique. La prévalence du SAHOS chez les patients atteints de fibrillation auriculaire (FA) varie de 32 à 85 % selon les études les plus récentes.
Objectif : Déterminer la prévalence et la sévérité du SAS chez une population suivie pour FA non valvulaire, et d'identifier ses facteurs prédictifs.
Méthodes : Nous avons réalisé une étude transversale, incluant des patients suivis pour FA. Les patients ayant des antécédents de SAHOS n'ont pas été inclus. Tous les patients ont eu un dépistage clinique du SAHOS et ont subi une polysomnographie.
Résultats : Nous avons inclus 100 patients dans cette étude. Le SAHOS a été confirmé chez 90% des patients atteints de FA. Le SAHOS était léger dans 32%, modéré dans 27% et sévère dans 31% des cas. Les caractéristiques cliniques étaient comparables entre les patients avec et sans SAHOS. Les facteurs prédictifs indépendants du SAHOS chez les patients atteints de FA étaient un âge supérieur à 61 ans (p = 0,029), une durée de FA supérieure à 2 ans (p = 0,04) et les ronflements (p = 0,01).
Conclusions : Le SAHOS a été diagnostiqué chez 90% des patients atteints de FA. Ainsi, un dépistage systématique du SAHOS pourrait être une approche pertinente étant donné sa prévalence élevée et ses implications thérapeutiques. Le ronflement, l'âge supérieur à 61 ans et la durée de la FA de plus de 2 ans étaient indépendamment associés au SAHOS.
Mots clés : syndrome d'apnées hypopnées obstructives du sommeil, fibrillation auriculaire, polysomnographie, prévalence, facteurs prédictifs

SUMMARY

Background: Obstructive Sleep Apnea Syndrome (OSAS) is a common but often under diagnosed condition that constitutes a real public health problem. The prevalence of OSAS in atrial fibrillation (AF) patients ranges from 32 to 85% according to recent studies.
Aim: To determine the prevalence and severity of OSAS in a population followed for non-valvular AF (NVAF), and to identify OSAS's predictive factors in this population.
Methods: A cross-sectional study was conducted, including successive patients followed for NVAF. Patients with a known history of OSAS were not included. All patients had a clinical screening for symptoms suggestive of OSAS and underwent an ambulatory sleep study.
Results: We included 100 patients in this study. OSAS was detected in 90% of NVAF patients. The average apnea-hypopnea index (AHI) was 21.6 ± 13.6 e/h. OSAS was mild in 32%, moderate in 27% and severe in 31% of cases. Clinical characteristics were comparable between patients with and without OSAS. The multivariate analytical study concluded that independent predictive factors of OSAS in AF patients were an age greater than 61 years (p=0.029), AF duration more than 2 years (p=0.04) and snoring (p=0.01).
Conclusions: OSAS was diagnosed in 90% of NVAF patients. Thus, a systematic screening for OSAS in AF patients may be a relevant approach given its high prevalence in this population and its therapeutic implications. Snoring, age greater than 61 years, and AF duration more than 2 years were independently associated with OSAS in our study.
Keywords: Obstructive sleep apnea syndrome; atrial fibrillation; ambulatory sleep test; OSAS prevalence; OSAS predictors.

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a common but often underdiagnosed condition, affecting about 4-5% of the adult population (1). It represents a real public health problem due to its frequency and its implication in several cardiovascular diseases (2-5).

A close relationship between OSAS and heart rhythm disorders, especially atrial fibrillation (AF) has been suggested in several studies (6). OSAS seems to induce hemodynamic, dysautonomic and inflammatory changes, which can lead to structural and electrical cardiac remodeling, substrates of AF.

Although there seems to be a pathophysiological link that can explain the relationship between OSAS and FA, it is only recently that epidemiological studies have shown an important association between these two pathologies independently of common risk factors (7). However, the prevalence of OSAS in AF patients is variably reported between 32 and 85% (7-14).

Given the OSAS negative impact on AF, and the uncertainty as to the precise nature of the relationship between these two pathologies, we sought through this work to assess the prevalence and severity of OSAS in a population followed for non-valvular AF (NVAF) and to study the possible predictive factors of OSAS in this population.

METHODS

Study design

This study was a cross-sectional analytic one, performed in the Cardiology department, over a period extending from January 1st, 2017 to October 1st, 2017.

Study Population

The enrolment involved randomly selected NVAF patients, aged over eighteen years and followed up in the outpatient consultation. Only patients, in whom the diagnosis of AF was documented, were included (15,16). Non-inclusion criteria were valvular AF (17) and those with a known history of OSAS.

Data collection

Data related to demographic, clinical characteristics and AF data (duration, class and AF effect on quality of life assessed by the EHRA classification (18)) were recorded for each patient. The functional signs suggestive of OSAS were collected. The importance of daytime sleepiness was particularly assessed by the Epworth sleepiness scale (19). Daytime sleepiness was considered excessive if the Epworth score was greater than 10 (20,21). The Berlin questionnaire was used to assess the clinical probability of OSAS (22,23), which included 10 questions divided in three categories. A Berlin score ≥ 2 indicated a high probability of OSAS and thus was considered as positive.

All patients were subjected to clinical examination (particularly anthropometric measurements) and ambulatory sleep test which was reviewed and approved by a sleep specialist. Apnea-Hypopnea Index (AHI) was defined as the number of apneas and/or hypopneas per hour.

According to international guidelines, diagnosis of OSAS is made when AHI is greater than 5 events per hour (e/h) (24). The latter index was also used to stratify the disease severity: mild with AHI ranging between 5 and 14 e/h, moderate with AHI between 15 and 29 e/h and severe with AHI ≥30 e/h (24).

We divided the study population into two groups: Group with an AHI ≥ 5 e/h (OSAS +) and Group with an AHI <5 e/h (OSAS -), and we compared them according to demographic and clinical characteristics.

Statistical analysis

The data were analyzed using SPSS statistical software (version 23.0)

Percentages were calculated to assess qualitative variables. Mean values and standard deviations, median and interval quartile range (IQR) were determined for the quantitative variables. The differences between patients with and without a diagnosis of OSAS were assessed by the independent sample t test for continuous variables and the chi-square test or Fischer's exact test for categorical variables. The search for OSA predictive factors in a univariate study, was carried out by calculating the Odds ratio (OR). For the Odds ratio calculation, we transformed the quantitative variables into qualitative variables with two modalities and we established ROC (Receiver Operating Characteristics) curves.

In order to identify the risk factors independently related to the event, a stepwise multivariate logistic regression

analysis was conducted to calculate adjusted Odds ratios. In all statistical tests, the significance level was set at 0.05.

Ethical approval

The study was conducted after free and informed consent of the participants. All participants were informed of the anonymity and confidentiality of their responses at the time of the investigation.

RESULTS

Population characteristics and polygraphic data

During the study period, 100 patients with NVAF were included. The mean age was 66.4 ± 9.7 years. Forty-five patients were male, and 55 patients were female.

The demographic and clinical characteristics of the study sample are shown in **table 1**.

Table 1: Clinical characteristics of study participants with a comparison between patients with and without OSAS

Characteristics	General population (N=100)	OSAS (+) (N=90)	OSAS (-) (N=10)	P
Demographic characteristics				
Age*	66.4 ± 9.7	67.6 ± 8.6	56.1 ± 13	**0.006**
Male gender	45	41 (45%)	4 (40%)	0.7
Cardiovascular risk factors				
Overweight/ Obesity	76	69 (76.6%)	7 (70%)	0.7
Hypertension	72	66 (73.3%)	6 (60%)	0.37
Dyslipidemia	45	41 (45.5%)	4 (40%)	0.7
Diabetes	31	26 (28.8%)	5 (50%)	0.17
Tabacco	25	24 (26.6%)	1 (10%)	0.47
Anthropometric characteristics				
Body mass index (Kg/m²)	28.5 ± 4.8	28.6 ± 4.9	27.7 ± 3.9	0.58
waist circumference (cm)	107.5 ± 12.6	107.9 ± 12.9	103.9 ± 9.5	0.31
Neck Circumference (cm)	38.8 ± 4.9	38.8 ± 4.9	38.4 ± 4.8	0.62

OSAS: obstructive Sleep Apnea Syndrome * p<0.05

AF was paroxysmal in 24 patients, persistent in 6 patients and permanent in 70 patients.

AF duration ranged from 6 months to 27 years, with a median value of 4.3 years. The effects of AF on quality of life, assessed by the EHRA classification, are reported in **Table 2**.

Table 2: Comparison of AF characteristics between groups with and without OSAS

Characteristics	General population (N=100)	OSAS (+) (N=90)	OSAS (-) (N=10)	P
AF duration* (years)	4.36	4.38	4.1	**0.02**
EHRA scale				
Asymptomatic (EHRA I)	18	14 (15.6%)	4 (40%)	0.056
Symptomatic (EHRA II, III, IV)	82	76 (84.4%)	6 (60%)	
AF clinical form				
Paroxystique	24	20 (22.2%)	4 (40%)	0.36
Persistent	6	6 (6.6%)	0	
Permanant	70	64 (71.1%)	6 (60%)	

EHRA : European Heart Rythm Association ; AF : atrial fibrillation ; OSAS : obstructive sleep apnea syndrome * p<0.05

The most common nocturnal sign in our population was snoring in 87 patients. The daytime symptomatology was dominated by daytime sleepiness which was found in 80 patients with an average of Epworth score of 10.3 ± 4.1. Excessive daytime sleepiness was reported in 54 patients.

According to the Berlin questionnaire, OSAS was very likely in 64% of patients.

After the sleep study, 90% of patients were found to have OSAS. The average AHI was 21.6 ± 13.6 e/h with extremes ranging from 1.1 to 54 e/h. Thirty-two patients had mild OSAS (32%), 27 patients (27%) had moderate OSAS and 31 patients (31%) had severe OSAS. Data relating to the ambulatory sleep monitoring and symptoms due to OSAS are described in **Table 3**.

Table 3: Comparison of symptoms suggestive of OSAS and clinical probability scores in patients with and without OSAS

Symptoms	General Population (N=100)	OSAS (+) (N=90)	OSAS(-) (N=10)	P
Nocturnal symptoms				
Snoring*	87	81 (90%)	6 (60%)	**0.024**
Sleep disorders	60	56 (62.2%)	4 (40%)	0.17
Nocturia	56	50 (55.5%)	6 (60%)	0.78
Daytime symptoms				
Daytime sleepiness Epworth score Epworth score > 10	80 10.3±4.1 54	73(81%) 10.5±4.1 51 (56%)	7(70%) 9±4.5 3 (30%)	0.4 0.2 0.1
Memory impairment	73	67 (74.4%)	6 (60%)	0.33
Morning fatigue	66	60 (66.6%)	6 (60%)	0.67
Cognitive impairment	41	38 (42.2%)	3 (30%)	0.45

OSAS : Obstructive sleep apnea syndrome * p<0.05

Comparison of clinical characteristics between patients with and without OSAS

Patients with OSAS were older than non-apneic patients (67.6 ± 8.6 years versus 56.1 ± 13 years) with a statistically significant difference (**p = 0.006**).

There was no significant difference between the two groups regarding the gender distribution, cardiovascular risk factors nor anthropometric parameters.

Details of clinical characteristics for both groups are reported in **Table 1**.

Comparison of AF characteristics in patients with and without OSAS

We noted a tendency to have more paroxysmal AF in the group without OSAS than in the group with OSAS (40% versus 22%, p = 0.36). Patients with OSAS were more likely to be symptomatic (EHRA II, III and IV) than those without OSAS (84.4% versus 60%, p = 0.056). The duration of AF was significantly longer in the OSAS (+) group (4.38 years; median: 3 years; IQR: 3 versus average: 4.1 years; median: 1 year; IQR: 2; **p = 0.02**).

The comparison of AF characteristics between the two groups is shown in **Table 2**.

Comparison of functional signs suggestive of OSAS in patients with and without OSAS

Among the nocturnal symptoms, snoring was found in 90% of patients with OSAS and in 60% of patients without OSAS with a statistically significant difference (**p = 0.02**). The other nocturnal signs and the daytime symptomatology were comparable between the two groups. The mean Epworth score was higher in patients with OSAS (10.5±4.1 vs 9±4.5) but the difference was not significant (p=0.2). The Epworth score had a sensitivity of 56.7% and a specificity of 70% to predict OSAS.

The Berlin score concluded that OSAS was very likely in 34% of apneic patients and 50% of non-apneic patients without a statistically significant difference. The sensitivity and the specificity of this test to predict OSAS were 34.4% and 50% respectively.

Table 3 summarizes the symptoms suggestive of OSAS and clinical probability scores in the two groups.

Clinical predictors of OSAS in NVAF patients

– *Univariate analysis*

We determined from the ROC curve that an age beyond 61 years was associated with a significant increase in OSAS prevalence (95.8% in OSAS (+) group versus 75% in OSAS (-) group, **p = 0.005**) with a sensitivity of 76.7% and a specificity of 70%.

We also objectified from the ROC curve, that an AF duration greater than 2 years was significantly more associated with diagnosis of OSAS (82.2% in OSAS (+) versus 40% in OSAS (-); **p = 0.007**) with a sensitivity of 82.2% and a specificity of 60%.

The univariate study's results are summarized in the **table 4**.

– *Multivariate analysis*

Multivariate regression analysis revealed that age > 61 years, snoring and AF duration > 2 years were independent predictors of OSAS (**table 4**).

Table 4 : Univariate and multivariate analysis of OSAS's pedictors in NVAF patients

Variables	P	Odds Ratio [OR]	CI (95%)
Univariate analysis			
- Age > 61 years*	**0.005**	7.66	1.820 – 32.294
- AF duration > 2 years*	**0.007**	6.93	1.753 – 27.458
- EHRA symptoms	0.056	3.62	0.904 – 14.496
- Snoring*	**0.024**	6	1.421 – 25.335
- Epworth ≥ 10	0.18	3.05	0.741 – 12.564
Multivariate analysis			
- Age > 61 years*	0.029	12.8	1.297 – 127.742
- AF duration > 2 years*	0.044	6.4	1.049 – 39.867
- Snoring*	0.019	18.9	1.623 – 221.13

EHRA : European Heart Rythm Association ; AF : atrial fibrillation ; CI: Confidence interval * p<0.05

Prevalence of OSAS in NVAF patients

In the present study, the prevalence of OSAHS was 90% in patients followed for NVAF, which is higher than previously reported in the literature (7-14). The average AHI in our study was 21.6 ± 13.6 e/h of sleep and severe OSAS was found in 31% of patients.

Several observational studies have shown frequent coexistence of AF and OSAS (7,9-14). However, the prevalence of OSAS in AF patients is variably reported and is estimated to be between 32 and 85%. This heterogeneity of results is largely explained by the difference in the choice of the AHI threshold to make the diagnosis of OSAS. In this study, the high prevalence of OSAS among NVAF patients could be also explained by our relatively elderly population with a high percentage of hypertensive and obese patients.

A prospective case-control study conducted by Gami el al. (7) involving 463 individuals showed that almost half of the patients presenting with AF were at risk of developing a OSAS reflecting a strong association between these two diseases (OR: 2.19; CI 95%: 1.4 - 3.42) independently of age, BMI, hypertension, diabetes or heart failure. The sensitivity and specificity of Berlin questionnaire remain insufficient to use it as a diagnostic tool which explains the low percentage of OSAS in this study compared to our study.

The results of Gami et al. (7) were supported in 2008 by another study conducted by Stevensen et al. (10), who reported in their study enrolling 90 patients, that 62% of patients with AF had nocturnal respiratory disorder compared to 38% in the control patients (p = 0.01). It is clearly evident that the found prevalence of OSAS in this population is lower than that of our study, which could be largely attributed to the threshold value of AHI used to retain the diagnosis of OSAS which was above 15 events per hour instead of an AHI threshold ≥5, threshold chosen to confirm the diagnosis of OSAS based on the criteria of the American academy of sleep medicine (24).

Braga et al. (11) followed in a prospective study, 52 patients with chronic AF and showed that patients with chronic AF had more nocturnal respiratory disorders than a subgroup of the population without arrhythmia (81.6% versus 60% ; p = 0.03), regardless of the usual common risk factors.

Szymanski et al. (12) studied the prevalence of OSAS in a population of 266 patients referred for AF ablation and concluded that OSAS was present in 45.5% of patients. This low percentage compared to that reported in the littérature and in our study could be explained by a relatively younger population.

More recently, a Japanese study conducted by Kohno et al. (13) in 197 patients referred for AF ablation found a remarkably high prevalence of OSAS (68.5%) which was lower compared to that reported in our study. These results could be explained by the anthropometric differences between studies (Body Mass Index : 25 ± 3 Kg/m2 in this study versus 28 to 31 Kg/m2 in various studies).

A recent study by Abumuamar et al. (9) including 100 AF patients, found an OSAS prevalence of 85%. These results joint those of our study, thus highlighting the high prevalence of OSAS in AF patients in whom the diagnosis of OSAS seems to be under-estimated.

There is undoubtedly increasing evidence of an association between AF and OSAS, which is based on a pathophysiological relationship establised by several authors (25). Some of these possible links include effects on intrathoracic pressure (26-28), impaired autonomic nervous control (26,29-31), and the role of inflammation and oxidative stress (32). It is probably the contribution of these multiple factors, rather than a single mechanism, that may ultimately contribute to the association of OSAS and AF

OSAS predictors in AF patients

In the present study, multivariate analysis concluded that snoring, age greater than 61 years (p=0.029 ; adjusted OR :12.8, $CI_{95\%}$:1.297 – 127.742) and AF duration greater than 2 years were independently associated with OSAS in AF patients.

Few studies have identified the predictors of OSAS in the NVAF population.

Age is a well-known OSA risk factor in the general population (33), as shown by studies of Kim et al. (34) and Sforza et al (35). Szymanski et al. (12) found in their study that patients with OSAS were older than non-apneic patients (59.6 ± 8 versus 56.0 ± 11 years; p = 0.02).

The study of Abumuamar et al. (9), had retained that age was an independent OSAS predictive factor (OR: 1.05, $CI_{95\%}$: 1.01-1.09) even after adjustment for sex and BMI. Furthermore, they had deduced that an age ≥ 60 years represented the threshold value beyond which SAOS was very likely (Odds Ratio=12; p= 0.003).

Increasing prevalence and severity of OSA in the older age group of patients with AF may be attributed to the effects of advanced age on the structure and function of the upper airways. These effects include atrophy of pharyngeal muscles, increased fat deposition, and lengthening of the soft palate, which all make the collapse of the upper airways during sleep more likely (36).

Furthermore, in the present study, we objectified that AF duration >2 years was significantly more associated with OSAS (82.2% versus 40%, p=0.007) and was an independent factor of OSAS (p=0.04, adjusted OR: 6.4; $CI_{95\%}$:1.04-39.86). The fact that an AF duration greater than 2 years represented an independent OSAS predictive factor, could be explained by a more advanced evolution of atrial remodeling when AF is old with a more frequent association of chronic forms, which are more associated with OSA according to some authors (12).

Study limitations

The present study is a small scale one mainly because of limited accessibility to polysomnographic investigation which contributed to limit the population's number and to prolong the study duration. Moreover, this study was subjected to selection bias: Although consecutive non selected patients were recruited, these patients were recruited with generally older patients with a high percentage of hypertension and obesity, which can influence the results, notably the high prevalence of OSAS observed in our population.

CONCLUSIONS

The present study demonstrated that OSAS was very common among NVAF patients, a finding similar to that of previous studies suggesting a strong association between OSAS and AF. Systematic screening for OSAS in NVAF patients is therefore a relevant approach given its high prevalence in this population and its prognostic impact. However, the problem of the polygraphy's cost arises in addition to the absence of reliable clinical scores that can sort the patient who should benefit from this investigation. Based on the results of our study, these scores could have as criteria the presence of snoring, an age greater than 61 years, and an AF duration of more than 2 years. Other large-scale, epidemiologically powerful studies are needed to confirm these criteria and validate this proposition.

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