

Original Article

Sleep-disordered breathing and chronic atrial fibrillation

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Abstract

Background: Little has been known about the prevalence of sleep apnea in patients with atrial fibrillation (AF). Studies have suggested that the prevalence of AF is increasing in patients with sleep-disordered breathing. We hypothesize that the prevalence of OSA is higher in chronic persistent and permanent AF patients than a sub-sample of the general population without this arrhythmic disorder.

Objective: Evaluate the frequency of Obstructive Sleep Apnea in a sample of chronic AF compared to a sub-sample of the general population.

Methods: Fifty-two chronic AF patients aged (60.5 ± 9.5 , 33 males) and 32 control (aged 57.3 ± 9.6 , 15 males). All subjects were evaluated by a staff cardiologist for the presence of medical conditions and were referred for polysomnography. The differences between groups were analyzed by ANOVA for continuous variables, and by the Chi-square test for dichotomous variables. Statistical significance was established by $\alpha = 0.05$.

Results: There were no differences in age, gender, BMI, sedentarism, presence of hypertension, type 2 diabetes mellitus, abdominal circumference, systolic and diastolic blood pressure, and sleepiness scoring between groups. Despite similar BMI, AF patients had a higher neck circumference compared to control group (39.9 cm versus 37.7 cm, $p = 0.01$) and the AF group showed higher percent-age time of stage 1 NREM sleep (6.4% versus 3.9%, $p = 0.03$).

Considering a cut-off value for AHI ≥ 10 per hour of sleep, the AF group had a higher frequency of OSA compared to the control group (81.6% versus 60%, $p = 0.03$). All the oxygen saturation parameters were significantly worse in the AF group, which had lower SaO₂ nadir (81.9% versus 85.3%, $p = 0.01$) and mean SaO₂ (93.4% versus 94.3%, $p = 0.02$), and a longer period of time below 90% (26.4 min versus 6.7 min, $p = 0.05$).

Conclusion: Sleep-disordered breathing is more frequent in chronic persistent and permanent AF patients than in age-matched community dwelling subjects.

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Keywords: Atrial fibrillation; Sleep apnea; Sleep-disordered breathing

1. Introduction

The prevalence of atrial fibrillation (AF) is 0.4% in the general population and 6% for those over 80 years

of age [1]. A recent population study estimated that the number of Americans afflicted by AF will increase from the current 2.3 million to more than 10 million by 2050 [2].

Obstructive sleep apnea affects 17–24% of American adults [3], and a high prevalence of obstructive sleep apnea has been found in patients with AF [4]. The estimated prevalence of undiagnosed obstructive sleep apnea (OSA) is up to 5% for adults in Western countries

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[3]. OSA induces intermittent hypoxemia, carbon dioxide retention, abrupt surges in arterial pressure, sympathetic activation, and changes in autonomic nervous tone that could contribute to the development of AF [5,6].

However, little is known on the prevalence of sleep apnea in AF patients. Recent cross-sectional studies have suggested that AF prevalence may be increasing in patients with sleep-disordered breathing and coexisting heart failure or recent coronary artery bypass surgery, suggesting that sleep apnea may contribute to arrhythmogenesis [7–9]. The only study that compared the prevalence of OSA in patients with lone AF to that in community control subjects found that the proportion of lone AF patients with moderate or severe OSA in a sample was more than twice the control group rate (11.9% versus 5.4%), but this was not statistically significant ($p = 0.22$) [10]. To our knowledge, there are no studies assessing sleep-disordered breathing using polysomnography that included only patients with chronic AF and excluded patients with sinus rhythm.

We hypothesize that the prevalence of OSA is higher in chronic persistent and permanent AF patients than in a sub-sample of the general population without this arrhythmic disorder.

2. Methods

2.1. Population

From July 2006 to January 2007, 57 consecutive patients were screened in the AF clinic at the Cardiology Section, Federal University of Sao Paulo, to participate in this study. The inclusion criterion was chronic persistent and permanent AF, defined as non-self terminating arrhythmia requiring electrical cardioversion to obtain sinus rhythm and patients in whom cardioversion has failed or has not been attempted, respectively [1,11]. Exclusion criteria were presence of previous stroke, patients with New York Heart Association class III or IV heart failure, left ventricular systolic dysfunction (left ventricular ejection fraction $\leq 40\%$), ischemic heart disease or acute myocardial infarction, chronic obstructive pulmonary disease (diagnosed from respiratory function test), thyroid, renal or hepatic disease, smoking more than 5 cigarettes a day, use of psychoactive or other drugs that could influence breathing patterns. Five patients (8.7%) were excluded because they had clinical evidence of a previous stroke. All AF patients were taking one or more of the following drugs: beta-blockers, calcium channel blockers, ACE inhibitors, diuretics, oral antiagregant, or anticoagulants. The final sample was 52 patients with atrial fibrillation rhythm (aged 60.5 ± 9.5 , 33 male). All patients were submitted to electrical cardioversion in order to restore sinus rhythm after data collection. Twenty patients, (38%) that

returned to normal sinus rhythm by electrical cardioversion, were classified as chronic persistent AF. The others (62%) were classified as a chronic permanent AF.

Control subjects were taken from a sample of an epidemiological study on sleep disorders in the general population of the city of Sao Paulo, Brazil (Epidemiologic Sleep Study – EPISONO). This is an on going epidemiological survey assessing sleep and polysomnographic characteristics of a representative sample of a Sao Paulo population including subjects older than 20 years.

The sampling frame consisted of a random sex- and age-stratified sample of the population. All these subjects were referred to the sleep center and underwent polysomnography. We studied the first 32 individuals from the EPISONO database, aged 50–65 years old, 15 males, mean age 57.3 ± 9.6 , and with BMI ranging from 22 to 38 kg/m^2 ($30.0 \pm 3.8 \text{ kg/m}^2$) in order to match our AF patients. The absence of atrial fibrillation was determined during 24-hour Holter monitoring and clinical evaluation.

The local ethics review committee approved the protocol, and all participants signed an informed consent form.

2.2. Study design

After signing the informed consent, patients were evaluated by a staff cardiologist at the Cardiology Division for the presence of medical conditions, smoking habits and sedentary lifestyle, (defined as the absence of a period of physical activity lasting at least 10 successive minutes during a typical week) [12]. Subjects also fulfilled the Epworth Sleepiness Scale (ESS) [13].

To exclude other severe cardiac and pulmonary diseases, 24-hour Holter monitoring, echocardiography, a myocardial radionuclide stress test, and respiratory function tests were performed. All subjects had a blood sample taken to analyze thyroid (serum thyroid-stimulating hormone and serum-free thyroxine), renal (creatinine clearance), and hepatic function (serum aspartate aminotransferase, alanine aminotransferase, and prothrombin time). Those subjects with negative findings (52 of 57) were submitted to baseline nocturnal polysomnography preceded by a night of adaptation to the sleep laboratory.

All control subjects underwent the same evaluation procedure as AF patients, except echocardiography. They were matched by age, gender, and body mass index (BMI).

2.3. Polysomnography

Bedtime was based on each patient's habits, and at least 7 h recording time was obtained. Data were collected from an electroencephalogram (at positions C3–A2, C4–A1, and O1–A2 of the International 10–20 Sys-

tem), a bilateral electrooculogram, a submental electromyogram, and an electrocardiogram (modified V2 lead). Respiration was monitored as follows: airflow was measured with a nasal cannula/pressure transducer system (Pro-Tech Services Inc., Mukilteo, WA) and a mouth thermocouple; chest and abdominal efforts were measured with uncalibrated, inductive, respiratory plethysmographic belts; arterial oxygen saturation (SaO₂) was measured with pulse oximetry (Ohmeda Hatfield, Herts, England); snoring sounds were measured with a neck microphone, and body position movements were measured with a mercury gauge. Body position was determined by a sensor. Data analyses were collected using a 16-channel computerized sleep system (Embla digital system S7000, Embla Systems Inc., CO, USA). An experienced researcher blinded to the medical condition of the participants performed sleep scoring for the two polysomnograms obtained from each subject in accordance with predetermined parameters [14]. Total sleep time (TST) was defined as the time from the first to last recorded sleep period, excluding wakefulness. Arousals lasting more than 3 s, and the arousal index per hour of sleep were scored using the criteria of the American Sleep Disorders Association [15]. In accordance with the American Academy of Sleep Medicine Task Force parameters, apnea was defined as a period of breathing cessation, and hypopnea was defined as a 50% reduction in breathing amplitude or a reduction of less than 50% associated with a 3% desaturation of oxyhemoglobin or arousal. These events had to last at least 10 s [16]. The abnormal apnea hypopnea index (AHI) was here defined as the total number of apneas and hypopneas per hour of TST above 10 per hour of sleep, due to the advanced age of our subjects. The percentage of TST with oxygen saturation (SaO₂) below 90%, SaO₂ nadir, and mean SaO₂ were also measured.

2.4. Statistical analysis

The results are expressed as mean \pm SD. The differences between groups were analyzed by analysis of variance for continuous variables. A chi-square test was performed to compare frequencies of dichotomous variables. Statistical analyses were conducted using a commercially available software package (Statistica Version 6.0; StatSoft Inc., Tulsa, Okla). Statistical significance was established by $\alpha = 0.05$.

3. Results

3.1. Characteristics of the study population

Characteristics of the study population are outlined in Table 1. There were no differences in age, gender, body mass index (BMI), sedentary lifestyle, presence of hypertension, type 2 diabetes mellitus, abdominal cir-

cumference, systolic and diastolic blood pressure, and sleepiness scoring on the ESS. Despite similar BMI, AF patients had a larger neck circumference than the control group (39.9 cm versus 37.7 cm, $p = 0.01$; Table 1).

There was no recording of ventricular arrhythmia or AF/flutter in the control group, demonstrated by clinical evaluation, 24-hour Holter monitoring and polysomnography data. The left ventricular ejection fraction of the AF group was $58.3 \pm 12.8\%$ and the average diameter of the left atrium was 4.6 ± 0.75 cm.

3.2. Polysomnography assessment

3.2.1. Sleep variables

Table 2 shows the results of the sleep structure parameters. No significant differences appeared among the total sleep time (TST); sleep efficiency, arousal index, periodic leg movement (PLM), nonrapid eye movement (NREM) sleep stages 2 and 3–4, and rapid eye movement (REM) sleep. Compared to control subjects, the AF group had higher percentage time of stage 1 NREM sleep (6.4% versus 3.9%, $p = 0.03$).

3.2.2. Sleep respiratory parameters

On taking a cut-off value of AHI ≥ 10 per hour of sleep, the AF group had a higher prevalence of OSA compared to the control group (81.6% versus 60%, $p = 0.03$). Although there was no difference between the AF group and the control group on mean AHI (24.3 versus 19.1, $p = 0.16$), all SaO₂ parameters were significantly worse in the AF group: lower SaO₂ nadir (81.9% versus 85.3%, $p = 0.01$) and mean SaO₂ (93.4% versus 94.3%, $p = 0.02$) and a longer period of time below 90% (26.4 min versus 6.7 min, $p = 0.05$). Results are outlined in Table 3.

Table 1
Characteristics of AF patients and controls

Characteristics	AF group (<i>n</i> = 52)	Controls (<i>n</i> = 32)	<i>F</i> ; <i>p</i>
Mean age (years)	60.5 \pm 9.5	57.3 \pm 9.6	ns
Male sex ^a (<i>n</i>)	33	15	ns
Mean BMI	28.9 \pm 5.8	30.0 \pm 3.8	ns
Hypertension ^a (%)	64.4	50.0	ns
Systolic BP ^b (mmHg)	130.9 \pm 18.1	133.4 \pm 17.7	ns
Diastolic BP ^b (mmHg)	80.8 \pm 13.8	85.6 \pm 12.7	ns
Neck circumference (cm)	39.9 \pm 2.3	37.7 \pm 4.5	5.8; 0.01
Abdominal circumference (cm)	103.3 \pm 11.0	100.2 \pm 12.9	ns
Diabetes mellitus (<i>n</i>)	2	1	ns
Sedentary ^a (%)	50	58	ns
ESS	8.6 \pm 5.6	7.9 \pm 3.8	ns

One-way ANOVA; BMI, body-mass index; BP, blood pressure; ESS, Epworth Sleepiness Scale; LVEF, Left Ventricular Ejection Fraction; ns, non-significant.

^a Chi-square.

^b Mean of two measurements.

Table 2
Sleep structure parameters

Characteristics	AF group (<i>N</i> = 52)	Controls (<i>N</i> = 32)	<i>F</i> ; <i>p</i>
TST	325.9 ± 74.1	327.9 ± 81.1	ns
Sleep efficiency	72.5 ± 16.0	78.9 ± 14.4	ns
Arousal (Index/hour of sleep)	15.9 ± 7.6	15.2 ± 7.6	ns
Stage 1 (% TST)	6.4 ± 5.9	3.9 ± 2.6	4.6; 0.03
Stage 2 (% TST)	58.3 ± 10.9	56.0 ± 10.9	ns
Stage 3 and 4 (%TST)	18.1 ± 10.8	22.0 ± 10.7	ns
REM (% TST)	15.6 ± 7.5	17.5 ± 6.3	ns
REM latency (min)	128.3 ± 108.4	113.1 ± 69.1	ns
PLM	7.1 ± 17.2	5.2 ± 12.3	ns

One-way ANOVA; TST, total sleep time; REM, rapid eye movement; PLM, periodic leg movement/hour of sleep; ns, non-significant.

Table 3
Sleep respiratory parameters

Characteristics	AF group (<i>N</i> = 52)	Controls (<i>N</i> = 32)	<i>F</i> ; <i>p</i>
AHI	24.3 ± 16.5	19.1 ± 15.3	0.16
SaO ₂ nadir (%)	81.9 ± 5.8	85.3 ± 5.2	6.5; 0.01
Mean SaO ₂ (%)	93.4 ± 2.1	94.3 ± 1.5	5.0; 0.02
SaO ₂ < 90% (min)	26.4 ± 55.8	6.7 ± 12.3	3.6; 0.05
OSA prevalence (AIH ≥ 10) ^a (%)	81.6	60	0.03

One-way ANOVA; AHI, apnea hypopnea index (division the number of events by total study time in hours); SaO₂, oxygen saturation; OSA, obstructive sleep apnea; data are presented as mean (SD) or %.

^a Chi-square.

4. Discussion

This is the only study assessing the prevalence of OSA in a homogenous group of AF patients characterized by the persistent or permanent condition of the arrhythmia, excluding paroxysmal AF and sinus rhythm cases, which was not the case of other studies in the literature. In addition, we compared this AF and OSA association to a control group of the general population. We were careful to exclude possible confounding factors such as congestive heart failure, coronary artery disease, and hyperthyroidism by performing medical evaluation and 24-hour 12-channel Holter recordings in both groups.

The main finding of this study is that OSA is more frequent in AF patients than in age-matched community dwelling subjects.

We found a high prevalence of 81.6% OSA in our AF patient sample against 60% for the control group. A small number of studies have suggested a high OSA percentage in AF subjects [4,10,18]. However, our percentage was higher than other reports. This cannot be explained by differences in BMI or age, which are similar to those reported in the literature. A possible explanation is the use of more permissive respiratory-event scoring criteria, including hypopneas with a decrease in amplitude of flow and nasal pressure transducer <50%

and higher than 10% accompanied by an arousal or SaO₂ drop [17]. Moreover, when a higher cut-off value for mild OSA (AHI > 15 events per hour of sleep) was applied in two studies, the authors found a lower frequency of OSA, but it was still higher than controls [11,18]. Gami et al. [4] reported that the percentage of patients with OSA was significantly higher in the AF group than in the general cardiology patient's group (49% versus 32%, *p* = 0.0004), but the use of the Berlin questionnaire to identify patients with OSA may be seen as a limitation of the study, because overnight sleep studies are gold standard for the diagnosis of OSA. Additionally, the validation of the Berlin questionnaire in this study showed a mean apnea–hypopnea index of 56 in patients whom the questionnaire identified as having OSA, suggesting a more severe OSA population than our patients.

In our study we also focused on other respiratory parameters such as SaO₂ values during sleep. Despite the lack of difference in mean AHI between groups, we found that AF subjects presented significantly lower SaO₂ nadir, mean SaO₂, and longer periods with SaO₂ below 90%, suggesting more severe OSA than that of the control group. The lack of difference in AHI in our study could be partially attributed to the variability of the data.

Atrial fibrillation has a heterogeneous clinical presentation [1]. Porthan et al. [10] compared the prevalence of OSA in patients with lone AF to that in community subjects. Since paroxysmal AF was not an exclusion criterion, the possibility of sinus rhythm during polysomnography could influence the results. As far as we know, this is the first controlled trial on OSA detection in chronic AF. The restricted inclusion of patients with persistent and permanent AF, and not paroxysmal AF or patients in sinus rhythm, may have determined higher hemoglobin desaturation in our AF group, such as SaO₂ nadir and time spent below 90%.

Despite the higher prevalence of OSA, few changes were found in sleep structure parameters in the AF population. Arousal index, an index of sleep fragmentation, did not differ from the control group, but the percentage of sleep stage 1 non-REM sleep (light sleep) was higher in the AF group, while slow wave sleep and REM stage sleep were similar in both groups. Other indicators of sleep quantity such as total sleep time and sleep efficiency showed no differences between groups. These data suggest that persistent and permanent AF did not significantly affect sleep continuity compared to non-AF general population controls, except for the significant, but slight increase in sleep stage 1. Even though arousal index values are controversial, the values found in our groups of subjects apparently matched other reports [19,20]. Considering the mean age of our sample, and the two consecutive polysomnographic studies, this elevation, if present, is slight.

Kushida et al. [21] have reported that a large neck circumference is a risk factor for OSA. We found that the AF group had larger neck circumferences for similar abdominal circumferences and BMIs, which matches previous findings for AF patients and normal controls reported by Porthan et al. [10], and may suggest that OSA is a risk factor for AF.

Obstructive respiratory events during sleep are sometimes accompanied by central apneas in cardiac or neurological disease patients, particularly in those with heart failure [22]. Sin et al. [23] found that AF is one of most important risk factors for central sleep apnea in a population with congestive-heart-failure, along with age >60 years. We did not observe abnormal numbers of central apneas during sleep in the AF group, possibly due to the exclusion of patients with the New York Heart Association, heart failure class III and IV.

Although careful clinical evaluation excluded cardiac disease, a limitation of the present study is not performing echocardiography to analyze left atrial size and left ventricular ejection fraction in control subjects.

In spite of the weak level of evidence afforded by case-control studies in finding independent associations, the results of the present study suggest that OSA is much more frequent in AF patients than we might expect.

In summary, more attention should be paid to the combination of AF and OSA. This condition appears to be under recognized and it is suggested that questions about sleep and snoring be included in the clinical evaluation of suspected AF patients. Physicians assessing these cases should rule out the presence of OSA, since sleep-disordered breathing treatment may improve cardiovascular outcome. Finally, controlled studies aiming to assess the effect of treating both conditions should shed some light on the pathophysiology of this complex association.

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