

# Arrhythmia/Electrophysiology

## Association of Atrial Fibrillation and Obstructive Sleep Apnea

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**Background**—Obstructive sleep apnea (OSA) is associated with recurrent atrial fibrillation (AF) after electrocardioversion. OSA is highly prevalent in patients who are male, obese, and/or hypertensive, but its prevalence in patients with AF is unknown.

**Methods and Results**—We prospectively studied consecutive patients undergoing electrocardioversion for AF (n=151) and consecutive patients without past or current AF referred to a general cardiology practice (n=312). OSA was diagnosed with the Berlin questionnaire, which is validated to identify patients with OSA. We also assessed its accuracy compared with polysomnography in a sample of the study population. Groups were compared with the 2-tailed *t*, Wilcoxon, and  $\chi^2$  tests. Logistic regression modeled the association of AF and OSA after adjustment for relevant covariates. Patients in each group had similar age, gender, body mass index, and rates of diabetes, hypertension, and congestive heart failure. The questionnaire performed with 0.86 sensitivity, 0.89 specificity, and 0.97 positive predictive value in our sample. The proportion of patients with OSA was significantly higher in the AF group than in the general cardiology group (49% versus 32%,  $P=0.0004$ ). The adjusted odds ratio for the association between AF and OSA was 2.19 (95% CI 1.40 to 3.42,  $P=0.0006$ ).

**Conclusions**—The novel finding of this study is that a strong association exists between OSA and AF, such that OSA is strikingly more prevalent in patients with AF than in high-risk patients with multiple other cardiovascular diseases. The coinciding epidemics of obesity and AF underscore the clinical importance of these results. (*Circulation*. 2004;110:364-367.)

**Key Words:** sleep ■ fibrillation ■ risk factors ■ arrhythmia ■ hypertension ■ obesity

Atrial fibrillation (AF) is a growing public health concern and has been described as an emerging epidemic.<sup>1</sup> The age-adjusted prevalence of AF in the United States has tripled from the 1960s to late 1980s.<sup>2</sup> In the year 2000, approximately 2 million American adults had AF,<sup>3</sup> and this number is expected to exceed 5 million by 2050.<sup>4</sup> This trend is a cause for alarm given the significant morbidity, mortality, and economic costs associated with AF.<sup>5,6</sup>

Obesity, too, is recognized as a national and worldwide epidemic.<sup>7,8</sup> The prevalence of obstructive sleep apnea (OSA) is directly related to body mass index, and more than 40% of obese patients have OSA.<sup>9</sup> The parallel epidemiological phenomena of AF and obesity might reflect common risk factors or, alternatively, a physiological interaction of these conditions. OSA and AF share many risk factors and comorbidities, including male gender, hypertension, congestive heart failure, and coronary artery disease.<sup>10</sup> Studies in patients with congestive heart failure noted an increased prevalence of AF in those patients with sleep apnea.<sup>11,12</sup> The presence of sleep apnea was shown to predict predischarge AF after coronary bypass surgery.<sup>13</sup> Furthermore,

untreated OSA doubles the risk of recurrence of AF in patients after electrical cardioversion, and treatment of OSA with continuous positive airway pressure attenuates that risk.<sup>14</sup>

Although OSA and AF share numerous disease associations, the prevalence of OSA in patients with AF is unknown. Because OSA is significantly underdiagnosed,<sup>15</sup> and treatment of OSA lowers the risk of recurrent AF,<sup>14</sup> determining the prevalence of OSA in patients with AF is clinically important. We tested the hypothesis that the prevalence of OSA in patients with AF is higher than that in nonselected cardiology practice patients with risk factors for OSA but no past or current AF.

### Methods

#### Study Population

We prospectively assessed the risk of OSA in 524 patients. The AF group included 151 consecutive patients with AF or flutter referred to the Mayo Clinic Cardioversion Center for electrical cardioversion. The general cardiology group included 373 consecutive patients who were referred to a general cardiology practice for cardiovascular

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**TABLE 1. Characteristics of the Study Population**

	AF Patients (n=151)	General Cardiology Patients (n=312)	P
Male gender, n (%)	97 (64)	181 (58)	0.200
White race, n (%)	148 (98)	289 (93)	0.018
Age, y			
Mean±SD	71±12	68±14	0.078
Median, IQR	73 (66–78)	71 (60–78)	
Body mass index, kg/m <sup>2</sup>			
Mean±SD	29±6	29±6	0.617
Median, IQR	28 (24–32)	28 (25–33)	
Neck circumference, cm			
Mean±SD	41±5	40±5	<0.001
Median, IQR	41 (38–44)	39 (36–42)	
Hypertension, n (%)	99 (66)	215 (69)	0.441
Diabetes, n (%)	26 (17)	74 (24)	0.107
Coronary artery disease, n (%)	49 (33)	157 (50)	<0.001
Congestive heart failure, n (%)	28 (19)	38 (12)	0.068

IQR indicates interquartile range.

disease management. Sixty-one patients with past or current AF were excluded from the latter group. Characteristics of the study population are described in Table 1.

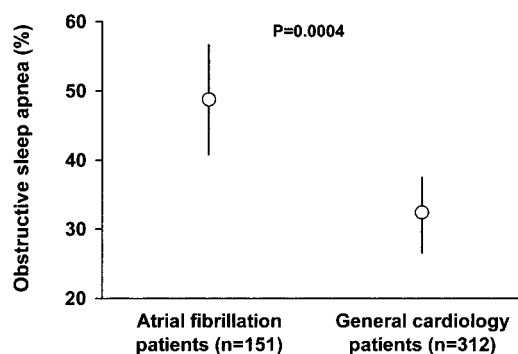
### Diagnosis of OSA

The presence of OSA was determined by the Berlin questionnaire, a validated instrument designed to identify individuals with OSA.<sup>16,17</sup> The questionnaire includes 1 introductory and 4 follow-up questions about snoring, 3 questions about daytime somnolence (including 1 concerning sleepiness while driving), and 1 question about history of hypertension. It also collects information about age, gender, race and ethnicity, height, weight, and neck circumference. Presence of OSA is determined by positive responses to at least 2 of the following 3 criteria: (1) persistent symptoms (>3 times per week) for at least 2 snoring questions, (2) persistent (>3 times per week) somnolence during daytime and/or while driving, and (3) history of hypertension or a body mass index >30 kg/m<sup>2</sup>. The questionnaire has high internal validity (Cronbach correlations 0.86 to 0.92) and performs accurately, with a sensitivity of 0.86, specificity of 0.77, and a positive predictive value of 0.89 in a primary care setting.<sup>17</sup>

### Validation of the Questionnaire

We validated the accuracy of the questionnaire in our study population by assessing its results in patients who had undergone formal sleep studies (n =44), which were performed by monitoring of the electroencephalogram, electrooculogram, submental and anterior tibial electromyograms, ECG, thoracoabdominal excursions (by respiratory inductive plethysmography), oronasal airflow (by thermistor or airflow pressure transducer), and arterial oxygen saturation (by pulse oximetry). An apnea was defined as a cessation of airflow for ≥10 seconds and hypopnea as a >50% reduction in airflow for ≥10 seconds, both in the setting of active ventilatory efforts. The apnea-hypopnea index was calculated as the mean number of apneas and hypopneas per hour of sleep. The diagnosis of OSA was established in accordance with the sleep study criteria recommended by the American Academy of Sleep Medicine.<sup>18</sup> The sensitivity, specificity, and positive predictive value of the questionnaire in our study sample was calculated using the sleep study results as the “gold standard.”

Patients with OSA identified by the questionnaire received a letter that described the finding and recommended consultation with their personal physician. Informed consent was obtained from all partic-



**Figure 1.** Proportion and 95% CI of patients with OSA. Prevalence of OSA is significantly higher in patients with AF than in patients without past or current AF in general cardiology practice (49% [95% CI 41% to 57%] vs 32% [95% CI 27% to 37%],  $P=0.0004$ ).

ipants, and the institutional committees on human research approved the study.

### Statistical Analysis

Characteristics of the study population were expressed as means (with SDs), medians (with interquartile ranges), and counts (with percentages). Differences between the AF group and the general cardiology group were tested by the unpaired *t* test or Wilcoxon rank-sum test for continuous variables and the  $\chi^2$  test for categorical variables. We calculated Bayesian confidence intervals (CI) for the proportions of patients with OSA in the AF group and the general cardiology group, and the proportions were compared by the  $\chi^2$  test. Statistical significance was established by  $\alpha=0.05$ . The OR and 95% CI for the association between OSA and covariates were assessed by univariate logistic regression. After adjustment for relevant covariates, multiple logistic regression modeled the adjusted OR and 95% CI for the association between AF and OSA.

## Results

### Characteristics of Study Population

Table 1 describes the characteristics of the study population. The AF Group and General Cardiology Group had statistically similar gender distribution, age, body mass index, and rates of diabetes, hypertension, and congestive heart failure. The AF Group had slightly larger neck circumference (41 versus 40 cm,  $P<0.001$ ) and a significantly lower rate of coronary artery disease (33% versus 50%,  $P<0.001$ ).

### Validation of Questionnaire

Compared with the gold standard of an overnight sleep study, the questionnaire performed with 0.86 sensitivity and 0.89 specificity and had a positive predictive value of 0.97 for OSA. The mean apnea-hypopnea index was 56 ( $\pm 34$ ) in patients whom the questionnaire identified as having OSA, compared with 1.4 ( $\pm 1.3$ ) in patients whom it identified as not having OSA ( $P<0.0001$ ).

### Association of AF and OSA

The proportion of patients with OSA was significantly higher in the AF group than in the general cardiology group (49% [95% CI 41% to 57%] versus 32% [95% CI 27% to 37%],  $P=0.0004$ ; Figure 1). Furthermore, to take into account potential misclassifications of OSA diagnoses by the questionnaire, we also analyzed a worst-case scenario in which the

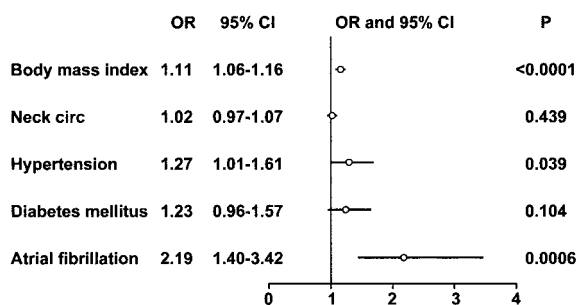
**TABLE 2. Unadjusted ORs and 95% CIs for OSA**

	OR	95% CI	P
Male gender	1.09	0.90–1.32	0.378
Age, y	0.99	0.97–1.00	0.085
Body mass index, kg/m <sup>2</sup>	1.12	1.08–1.16	<0.0001
Neck circumference, cm	1.11	1.06–1.15	<0.0001
Hypertension	1.28	1.04–1.57	0.019
Diabetes mellitus	1.33	1.08–1.69	0.008
Coronary artery disease	1.03	0.85–1.24	0.754
Congestive heart failure	1.06	0.81–1.38	0.669
AF	1.89	1.28–2.82	0.002

difference between groups was minimized by decreasing the number of OSA patients in the AF group by the false-positive rate (0.032) and increasing the number of OSA patients in the general cardiology group by the false-negative rate (0.143). Even then, the proportion of patients with OSA in the AF group was significantly higher than that in the general cardiology group (48% versus 37%,  $P=0.022$ ). Univariate analysis identified significant associations between OSA and body mass index, neck circumference, hypertension, diabetes mellitus, and AF (OR 1.89, 95% CI 1.28 to 2.83,  $P=0.002$ ; Table 2). In multivariate analysis, body mass index, hypertension, and AF remained significantly associated with OSA, and the OR was largest for AF (2.19, 95% CI 1.40 to 3.42,  $P=0.0006$ ; Figure 2).

## Discussion

The novel findings of the present study are that approximately half of patients with AF are likely to have OSA and that 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. The study also confirmed that established cardiovascular diseases, such as coronary artery disease and congestive heart failure, are accompanied by a high prevalence of OSA.<sup>19,20</sup> Furthermore, the prevalence of OSA in patients with AF was substantially greater than the prevalence of OSA in patients with established cardiovascular disease but without past or current AF.



**Figure 2.** Adjusted OR and 95% CI for association between AF and OSA. After adjustment for body mass index, neck circumference (neck circ), hypertension, and diabetes mellitus, AF is significantly associated with OSA (OR 2.19, 95% CI 1.40 to 3.42,  $P=0.0006$ ).

These findings support the concept that it is not only the associated conditions of OSA (most importantly hypertension) that may lead to AF, but there may be a unique interaction between the pathophysiologies of OSA and AF. In patients with OSA, intermittent hypoxemia, hypercapnia, chemoreceptor excitation, markedly increased sympathetic drive, and severe pressor surges,<sup>21</sup> all of which occur nightly for years if untreated, may initiate or predispose to AF. Hypoxemia and hypercapnia themselves are arrhythmogenic.<sup>22,23</sup> Nocturnal increases in sympathetic activation persist during wakefulness in patients with OSA,<sup>24</sup> and increased sympathetic drive is associated with AF.<sup>25,26</sup> The forceful ventilatory efforts against upper airway obstruction during apneas result in dramatic shifts in transmural pressures and measurable changes in cardiac chamber dimensions.<sup>27,28</sup> These acute structural changes may promote AF via the triggering of stretch-activated atrial ion channels.<sup>29</sup> In addition, severity of OSA is independently associated with elevated markers of systemic inflammation, including C-reactive protein.<sup>30</sup> C-reactive protein, in turn, is directly associated with an increasing burden of AF.<sup>31</sup>

Although these mechanisms are likely to explain the relationship between OSA and AF, the reverse paradigm may be true in some patients in whom atrial arrhythmias play a role in causing OSA. This concept is relevant to the finding that atrial overdrive pacing reduced the severity of sleep apnea in a small group of patients with sinus node dysfunction.<sup>32</sup> The pathophysiology is unclear but may relate to effects of atrial arrhythmias on cardiac afferent autonomic activity and central nervous system mechanisms that direct ventilatory control and airway muscle activity.<sup>33,34</sup>

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 the gold standard for the diagnosis of OSA. However, in addition to the questionnaire's established validity in a primary care setting,<sup>17</sup> we confirmed that it was extremely accurate in the present study population. We showed in a subgroup of our study population that the questionnaire predicted 86% of cases and that 97% of those predicted indeed had OSA by complete overnight sleep studies. The performance of the questionnaire was slightly better than in previous studies,<sup>16,17</sup> likely due to the higher prevalence of OSA in the present study sample. Even in a hypothetical worst-case scenario, in which we maximized potential misdiagnoses of OSA to minimize the difference in OSA prevalence between the groups, the proportions of patients with OSA in the AF group remained significantly higher than that in the general cardiology group. Thus, the questionnaire accurately and efficiently identified patients with OSA in a large sample of patients with a spectrum of cardiovascular diseases, and the general results of the study would be unchanged even if the performance of the questionnaire was biased to show no difference between the groups.

There are important clinical implications of the present study's finding that a striking proportion of patients with AF also have OSA, especially as the number of patients with obesity and AF grows. Given recent data about the increased recurrence of AF in patients with untreated OSA and the lower risk of recurrence with continuous positive airway

pressure therapy, it would be important to identify the large proportion of patients with AF who have OSA and are eligible for such treatment. The presence of OSA should be considered in all patients with AF, and screening might be warranted in patients with AF who are obese or hypertensive.

### Disclosure

Dr Somers is a past consultant for ResMed and Respirationics.

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