CHEST

Original Research

SLEEP DISORDERS

Sleep-Disordered Breathing and Excessive Daytime Sleepiness in Patients With Atrial Fibrillation

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Background: **An important consequence of sleep-disordered breathing (SDB) is excessive daytime sleepiness (EDS). EDS often predicts a favorable response to treatment of SDB, although in the setting of cardiovascular disease, particularly heart failure, SDB and EDS do not reliably correlate. Atrial fibrillation (AF) is another highly prevalent condition strongly associated with SDB. We sought to assess the relationship between EDS and SDB in patients with AF.**

Methods: **We conducted a prospective study of 151 patients referred for direct current cardioversion for AF who also underwent sleep evaluation and nocturnal polysomnography. The Epworth Sleepiness Scale (ESS) was administered prior to polysomnography and considered positive if the score was ≥ 11. The apnea-hypopnea index (AHI) was tested for correlation with the ESS, with a cutoff of ≥ 5 events/h for the diagnosis of SDB.**

Results: **Among the study participants, mean age was 69.1 ± 11.7 years, mean BMI was 34.1 ± 8.4 kg/m^2, and 76% were men. The prevalence of SDB in this population was 81.4%, and 35% had EDS. The association between ESS score and AHI was low ($R^2 = 0.014$, $P = .64$). The sensitivity and specificity of the ESS for the detection of SDB in patients with AF were 32.2% and 54.5%, respectively.**

Conclusions: **Despite a high prevalence of SDB in this population with AF, most patients do not report EDS. Furthermore, EDS does not appear to correlate with severity of SDB or to accurately predict the presence of SDB. Further research is needed to determine whether EDS affects the natural history of AF or modifies the response to SDB treatment.** ***CHEST 2012; 141(4):967–973***

Abbreviations: AF = atrial fibrillation; AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; CSA = central sleep apnea; DCCV = direct current cardioversion; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnea; SDB = sleep-disordered breathing

Sleep-disordered breathing (SDB), collectively encompassed by obstructive sleep apnea (OSA) and central sleep apnea (CSA), is increasingly associated with several common cardiovascular disorders, including hypertension,[1] heart failure,[2] myocardial infarction,[3] and atrial fibrillation (AF).[4] AF, the most common sustained arrhythmia that affects ~2.3 million adults in the United States,[5] is associated with both OSA and CSA. OSA has been implicated as both a cause of incident AF[4] and AF recurrence after direct current cardioversion (DCCV).[6] CSA has been shown to be common in samples of patients with AF with and without heart failure.[2,7] Because OSA appears to be common in patients with AF, affecting approximately one-half of this population,[4] and may be related to important outcomes, simple screening tools would be useful to guide referral to sleep centers.

An important, although not universal, consequence of SDB is excessive daytime sleepiness (EDS).[8] EDS affects ~12% of the general population.[9] The mechanisms that lead to EDS in patients with SDB may include nocturnal hypoxia,[10] repeated arousals from sleep, enhanced sympathetic tone,[11] or obesity.[12] EDS is most efficiently detected by the Epworth Sleepiness Scale (ESS), a validated questionnaire that inquires about the chance of dozing under real-life situations.[13]

Multiple clinical trials have shown that positive airway pressure therapy effectively improves EDS in patients with OSA.[14] There is emerging evidence that EDS may be an important predictor of improved cardiovascular outcomes associated with treatment of SDB.[15] For example, positive airway pressure trials in OSA have shown greater reductions in BP in those who are sleepy prior to treatment.[16,17] To further explore this relationship as well as to determine how the ESS performs as a screening tool for SDB in the AF population, we sought to characterize the relationship between EDS and SDB in a cohort of patients with AF.

Materials and Methods

Subjects

From June 2004 to April 2009 we conducted a prospective study of patients referred to the Mayo Clinic Center for Sleep Medicine for a sleep evaluation following DCCV treatment of AF. A total of 151 patients who underwent in-laboratory-attended polysomnography were included in the analysis. Echocardiography generally was performed prior to DCCV. This study was approved by the Mayo Clinic Institutional Review Board (IRB-#1646).

Daytime Sleepiness

To assess the degree of daytime sleepiness, all patients completed the ESS, a simple, self-administered, validated questionnaire used in the general population,[13] during their initial evaluation prior to the polysomnography. Possible scores ranged from 0 to 24 (the most sleepy); EDS was defined as an ESS score of ≥ 11.[13]

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Polysomnography

The diagnosis of SDB was established by attended polysomnography performed at the Mayo Clinic Center for Sleep Medicine and digitally recorded by a multichannel system (Nicolet Instrument Corp). We used an apnea-hypopnea index (AHI) cutoff of ≥ 5 events/h to diagnose SDB. Simultaneously recorded parameters included three-channel EEG, two-channel electrooculography, oronasal airflow by pressure transducer and thermocouple sensors, submental and limb electromyograms, ECG, transcutaneous pulse oximetry (Ohmeda 3740; GE Healthcare), thoracic and abdominal respiratory effort by inductance plethysmography, snoring by external microphone, and body position by closed-circuit video monitoring.

Scoring of sleep stages, disordered breathing events, oxygen desaturation, and periodic limb movement was performed by an experienced polysomnographic technician, and results were reviewed by a board certified physician in accordance with current American Academy of Sleep Medicine guidelines. Apneas were defined as cessation of airflow or a $>90\%$ reduction of airflow from baseline for ≥ 10 s. Hypopneas were defined as a reduction in airflow of $\geq 50\%$ for ≥ 10 s followed by an oxygen desaturation of $\geq 4\%$. Events were classified as central when the airflow criteria were met in the absence of respiratory effort as recorded by thoracic and abdominal inductance plethysmography and as obstructive when airflow criteria were met despite continued or increased respiratory effort. After classification, disordered breathing events were quantified by the AHI and reported as the mean number of events per hour. Subjects were considered to have CSA if the total AHI was ≥ 5 events/h with $\geq 50\%$ of disordered breathing events classified as of central origin or with classic Cheyne-Stokes pattern of respiration. Oxygen saturation was measured prior to and continuously during sleep and quantified by both the mean oxygen saturation and the proportion of sleep time spent with arterial oxygen saturation $>90\%$.

Statistical Analysis

Data are summarized as frequencies for categorical variables and mean ± SEM for continuous variables, unless otherwise noted. Group differences were evaluated by two-sided *t* test or Wilcoxon rank sum test, depending on distribution. Differences in proportions were tested by Fisher exact test. The ESS score also was treated as a continuous variable for data exploration.

Patients were stratified by different AHI cutoffs as having no SDB (<5 events/h), mild SDB ($\geq$5-15 events/h), moderate SDB ($>$15-30 events/h), or severe SDB (>30 events/h) (Fig 1), and

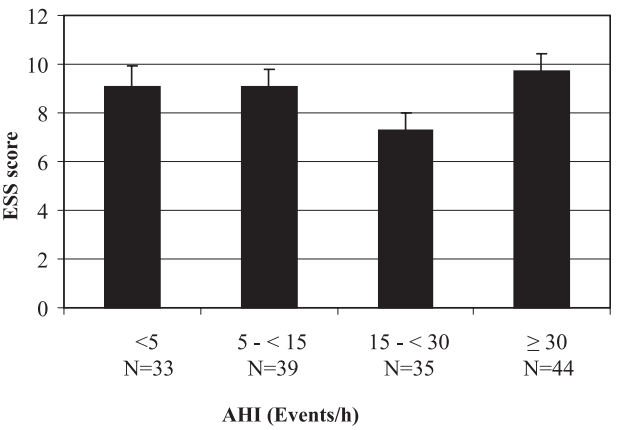

Figure 1. Mean ESS score of the population divided into different AHI cutoffs. AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale.

Table 1—*Subject Characteristics*

Characteristic	No EDS (n = 98)	EDS (n = 53)	*P* Value
Age, y	70.1 ± 1.2	67.1 ± 1.6	.13
Male sex	80.6	68.8	.08
BMI, kg/m²	33.6 ± 0.8	35.0 ± 1.1	.31
Ejection fraction, %	53.9 ± 1.3	57.8 ± 1.8	.08
Ejection fraction ≤ 40%	16.3	9.4	.24
LV diastolic dimension, mm	52.4 ± 0.7	52.4 ± 0.9	.97
LV systolic dimension, mm	36.3 ± 0.9	34.9 ± 1.1	.33
RV systolic pressure, mm Hg	39.2 ± 1.7	42.3 ± 2.3	.28
RA pressure, mm Hg	8.5 ± 0.5	8.7 ± 0.7	.81

Data are presented as mean ± SE or %. EDS = excessive daytime sleepiness; LV = left ventricle; RA = right atrium; RV = right ventricle.

the mean ESS was compared between these groups by analysis of variance. The sensitivity, specificity, positive predictive value, and negative predictive value of the ESS using cutoffs within the interquartile range of the ESS score distribution were calculated for prediction of SDB (≥ 5 events/h). Linear regression analysis was used to assess the association between AHI and ESS. The sensitivity, specificity, positive predictive value, and negative predictive value were used to evaluate the ability of an ESS score ≥ 11 to predict SDB using various AHI cutoffs. As a secondary analysis, the sensitivity, specificity, positive predictive value, and negative predictive value of the ESS using the conventional cutoff of ≥ 11 to predict SDB (≥ 5 events/h) were compared among men and women and in subjects aged ≥ 70 and < 70 years using logistic regression to test for a significant interaction. Analyses were performed with JMP, version 7 (SAS Institute Inc) statistical software. For all comparisons $P < .05$ was considered statistically significant.

Results

Demographic characteristics of all subjects according to the presence or absence of EDS are reported in Table 1. Mean age was 69.1 ± 0.9 years, mean BMI was 34.1 ± 0.7 kg/m², and 76% of the patients were men. The mean left ventricular ejection fraction was 55.3% ± 1.1%; only 14% of the subjects had a left ventricular ejection fraction of ≤ 40%. The overall prevalence of SDB was 81.4%. OSA, as defined by an AHI of ≥ 5 events/h, was present in 57% of the subjects; using an AHI cutoff of ≥ 15 events/h, the prevalence was 52.3%. Additionally, 13.9% of the patients had CSA, 10.6% had mixed sleep apnea, and 18.6% had normal polysomnography (Table 2). SDB was more common in men than in women (87.8% vs 61.1%, $P < .001$). The mean AHI was 23.1 ± 1.8 events/h in the whole population and 27.4 ± 2.0 events/h in those with SDB. On average, women had a lower mean AHI compared with men in the entire sample (15.5 ± 3.7 events/h vs 25.5 ± 2.0 events/h, $P = .02$) and among those with SDB (21.1 ± 3.8 events/h vs 28.8 ± 2.3 events/h, $P = .09$).

EDS was present in 35% of all subjects and did not differ by the presence or absence of SDB (31.3% vs 47.2%, $P = .08$) or among those with OSA, CSA, and mixed apnea (37.2% vs 19.1% vs 25.0%, $P = .34$). The correlation of total AHI and the ESS score was very low ($R^2 < 0.01$, $P = .64$). The mean ESS score was 8.9 ± 0.36 and did not differ by the presence or absence of SDB (8.9 ± 0.4 vs 9.0 ± 0.8, $P = .8$) or

Table 2—*Polysomnographic Findings of Patients With and Without EDS*

Characteristic	No EDS (n = 98)	EDS (n = 53)	*P* Value
AHI, events/h	23.5 ± 2.3	22.3 ± 3.1	.75
OSA	32 (62.8)	21 (37.2)	.53
CSA	17 (80.9)	4 (19.1)	.10
Mixed	12 (75.0)	4 (25.0)	.37
Normal PSG	15 (53.6)	13 (46.4)	.19
Total sleep time, min	180 ± 8.5	194 ± 11.6	.33
Sleep efficiency, %	68.4 ± 1.6	74.7 ± 2.2	.03
% Total sleep time > 90% SaO_2	88.0 ± 2.3	83.6 ± 3.1	.23
% Total sleep time stage 1	18.45 ± 1.5	18.45 ± 2.1	.99
% Total sleep time stage 2	54.7 ± 1.6	54.5 ± 2.1	.94
% Total sleep time stage 3/4	14.9 ± 1.4	15. 9 ± 1.9	.68
% Total sleep time stage REM	11.9 ± 0.9	11.1 ± 1.3	.62
AHI < 5 (n = 33)	54.6	45.4	.15
5 ≤ AHI < 15 (n = 39)	61.5	38.5	.6
15 ≤ AHI < 30 (n = 35)	85.7	14.3	< .01
AHI ≥ 30 (n = 44)	59	41	.33

Data are presented as mean ± SE, No. (%), or %. AHI = apnea-hypopnea index; CSA = central sleep apnea; OSA = obstructive sleep apnea; PSG = polysomnogram; REM = rapid eye movement; SaO_2 = arterial oxygen saturation. See Table 1 legend for expansion of other abbreviation.

Table 3—*ESS Scores and Prevalence of EDS Using Different AHI Cutoffs*

	AHI < 5	5 ≤ AHI < 15	15 ≤ AHI < 30	AHI ≥ 30	*P* Value
ESS score, mean ± SE	9.2 ± 0.8	9.2 ± 0.7	7.3 ± 0.8	9.7 ± 0.7	.12
ESS score ≥ 11, %	28.3	28.3	9.4	34.0	.03

ESS = Epworth Sleepiness Scale. See Table 1 and 2 legends for expansion of other abbreviations.

severity of SDB (no SBD, 9.2 ± 0.8; mild, 9.2 ± 0.7; moderate, 7.3 ± 0.8; severe, 9.7 ± 0.7; $P = .12$). Mean ESS did not differ between men and women in the entire study (8.7 vs 9.5, $P = .38$) or between men and women with SDB (8.7 ± 0.4 vs 9.4 ± 1.0, $P = .60$). The percentage of subjects with an ESS score ≥ 11 showed a significant ($P = .03$), although nonlinear trend (Table 3).The interquartile range of ESS scores was 5 to 12, and no ESS cutoff in this range appeared to function better than the standard cutoff of 11 (Table 4).

There was no significant difference in the mean AHI in patients with EDS compared with patients without EDS (22.3 ± 3.1 vs 23.5 ± 2.3, $P = .75$). Using an AHI cutoff of ≥ 5 events/h to diagnose SDB, the sensitivity and specificity of the ESS score to predict SDB were 32.2% and 54.5%, respectively, with a positive predictive value of 71.7% and negative predictive value of 18.8%; similar results were obtained using different AHI cutoffs (Table 5). The prevalence of EDS in patients with OSA (n = 86) was ~37%, and in patients with CSA (n = 21), it was 19%. Excluding all the patients with heart failure (n = 21), the prevalence of EDS slightly increased from 35% to 37%. No significant interaction was seen between the ESS and sex ($P = .66$) or age ($P = .18$), although the ESS showed a trend toward higher sensitivity in women and subjects aged ≥ 70 years and greater specificity in men and subjects aged < 70 years (Table 6).

Discussion

The present study demonstrates that SDB is highly prevalent in patients with AF referred for sleep evaluation following DCCV who, despite marked elevations in the AHI, generally do not report subjective daytime sleepiness. Furthermore, EDS does not correlate with the presence or absence of SDB. Given the very high prevalence of SDB in patients with AF, the lack of sleepiness cannot be used to rule out the presence of SDB.

The data suggest that typical symptoms such as EDS cannot be relied on as a marker of SDB in the AF population. Although the main results show a low sensitivity (32.2%) and specificity (54.5%) of the ESS using the standard AHI cutoff of 5 events/h for the diagnosis of SDB, similar results were obtained using a higher AHI cutoff of 15 events/h (sensitivity, 29.1%; specificity, 50.0%). Furthermore, using different cutoff values did not seem to significantly improve the performance of the ESS, nor did the ESS perform significantly better in men vs women or in older vs younger adults. These results suggest that clinicians should not exclude the possibility of SDB in patients with AF who do not have sleep-related complaints. A similar relationship has been reported in the heart failure and stroke population with SDB, where patients appear to infrequently report subjective sleepiness.[18,19] It has been speculated that the lack of sleepiness in patients with heart failure may be linked with increased sympathetic nervous activity.[20] Because heightened sympathetic tone has been associated with AF,[21] a similar mechanism may be involved in patients with AF.

A key question that remains to be clarified is whether these findings play a role in important outcomes in the AF population. Potential clues can be found from the literature describing other cardiovascular diseases. For example, there is evidence that the association between SDB and hypertension is stronger in patients

Table 4—*Performance of the ESS for SDB*

ESS Score	Sensitivity, %	Specificity, %	PPV, %	NPV, %
5	82.1 (74.4-87.9)	14.3 (5.7-31.5)	80.8 (73.0-86.7)	15.4 (6.2-33.5)
6	73.2 (64.7-80.2)	21.4 (10.2-39.5)	80.4 (72.0-86.7)	15.4 (7.2-29.7)
7	65.0 (56.3-72.9)	32.1 (17.9-50.7)	80.8 (72.0-87.4)	17.3 (9.4-29.7)
8	54.5 (45.7-63.0)	42.9 (26.5-60.9)	80.7 (71.0-87.8)	17.6 (10.4-28.4)
9	46.3 (37.8-55.1)	46.4 (29.5-64.2)	79.2 (68.4-86.9)	16.5 (9.9-26.1)
10	39.0 (30.9-47.9)	46.4 (29.5-64.2)	76.2 (64.4-85.0)	14.8 (8.8-23.7)
11	32.5 (24.9-41.2)	53.6 (35.8-70.5)	75.5 (62.4-85.1)	15.3 (9.5-23.7)
12	29.3 (22.0-37.8)	67.9 (49.3-82.1)	80.0 (66.2-89.1)	17.9 (11.8-26.3)

Data are presented as median (95% CI). SDB was defined as an AHI ≥ 5 events/h. NPV = negative predictive value; PPV = positive predictive value; SDP = sleep-disordered breathing. See Table 2 and 3 legends for expansion of other abbreviations.

Table 5—*Accuracy of the ESS as a Predictor of SDB*

AHI, Events/h	Sensitivity, %	Specificity, %	PPV, %	NPV, %
≥ 5	32.2 (24.4-41.1)	54.5 (38.0-70.2)	71.7 (58.4-82.0)	18.4 (11.9-27.2)
≥ 10	27.7 (19.6-37.4)	52.6 (39.9-65.0)	49.1 (36.1-62.1)	30.6 (22.4-40.3)
≥ 15	29.1 (20.3-39.9)	58.3 (46.8-69.0)	43.4 (31.0-56.7)	42.9 (33.5-52.7)
≥ 30	40.9 (27.7-55.6)	67.3 (57.9-75.4)	34.0 (22.7-47.4)	73.5 (64.0-81.2)

Data are presented as median (95% CI). See Table 2, 3, and 4 legends for expansion of abbreviations.

who report sleepiness than in those who do not.[15] Furthermore, data from controlled interventional trials suggest that subjects who are less sleepy show a smaller decrease in BP with continuous positive airway pressure (CPAP).[22,23] In a previous observational study, our laboratory reported that compliance with prescribed CPAP therapy for sleep apnea favorably alters the natural history of AF following electric cardioversion.[6] It is acknowledged that symptoms such as EDS likely promote compliance with CPAP therapy,[24,25] which may, therefore, lead to more complete eradication of the downstream effects of apnea. Further research is needed to determine whether EDS is an important modifier of cardiovascular outcomes in this population.

The present study confirms previous data showing a high prevalence of sleep apnea in patients with AF.[4,7,26] The fact that many do not have sleep-related complaints raises the question of how to manage such patients. As noted previously, some data suggest that there is little evidence showing that CPAP treatment affects cardiovascular outcomes in patients who are not sleepy. Furthermore, a significant portion of older adults may have an AHI > 5 events/h.[27] On the other hand, it is difficult to ignore the public health problem of AF, which is associated with complications such as stroke, heart failure, and death.[28] We have shown that patients with OSA who are successfully cardioverted but do not receive CPAP treatment may be at a twofold greater risk for recurrence of AF within 1 year.[6] Conceivably, recognition and treatment of SDB may directly affect maintenance of sinus rhythm and influence the likelihood of complications.

Further considerations include the logistics of identifying, diagnosing, and treating SDB in the AF population. Screening tools in SDB are not well standardized, and the use of questionnaires and nocturnal pulse oximetry are controversial. Snoring is very common but an insensitive marker of OSA.[29] EDS often has been used as a potential marker for the presence of undiagnosed sleep apnea. However, the present data suggest that EDS does not provide a valid indication of the presence or absence of occult sleep apnea. The role of screening tools in this patient population requires further study and validation. Furthermore, commonly used questionnaires suggesting the presence of sleep apnea should exclude the use of sleepiness as a scored variable because inclusion of this measure in any index would likely diminish the sensitivity and specificity of the overall index for patients with AF undergoing cardioversion.

The present findings have some limitations. The ESS questionnaire is considered to be a marker of subjective sleepiness, and we acknowledge its limited correlation with objective measures of sleepiness, such as the multiple sleep latency test.[30] In addition, its validity in a strictly referral population with cardiovascular disease is not entirely known. As a comparison, the prevalence of EDS in this sample exceeds estimates from population-based studies showing that 15% to 20% of persons in the community will score > 10 on the ESS.[31] Selection bias may have resulted in a higher prevalence of SDB than in the general population of patients with AF because our population was referred for sleep evaluation following DCCV. Finally, none of the patients were found to have other potential causes of EDS, such as narcolepsy, periodic limb movement disorder, and the idiopathic hypersomnia syndromes.

In summary, among patients with AF referred for cardioversion, there is a high prevalence of SDB,

Table 6—*Accuracy of the ESS as a Predictor of SDB in Different Subgroups*

Subgroup	Sensitivity, %	Specificity, %	PPV, %	NPV, %	*P* Interaction
Overall	32.5 (24.9-41.2)	53.6 (35.8-70.5)	75.5 (62.4-85.1)	15.3 (9.5-23.7)	…
Men	29.7 (21.7-39.2)	57.1 (32.6-78.6)	83.3 (68.1-92.1)	10.1 (5.2-18.7)	.66
Women	45.5 (26.9-65.3)	50.0 (26.8-73.2)	58.8 (36.0-78.4)	36.8 (19.1-59.0)	…
Aged < 70 y	40.7 (28.7-54.0)	57.9 (36.3-76.9)	73.3 (55.6-85.8)	25.6 (14.9-40.2)	.18
Aged ≥ 70 y	73.3 (55.6-85.8)	25.6 (14.9-40.2)	40.7 (28.7-54.0)	57.9 (36.3-76.9)	…

Data are presented as median (95% CI). A positive ESS was considered to be a score of ≥ 11, and SDB was defined as an AHI ≥ 5 events/h. See Table 2, 3, and 4 legends for expansion of abbreviations.

although most patients do not report EDS as measured by the ESS. Furthermore, EDS does not appear to correlate with severity of the SDB or to accurately predict the presence or absence of SDB in patients with AF. Further research is needed to determine whether EDS affects the natural history of AF or modifies the response to treatment of AF or SDB in this population.

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Dr Calvin: contributed to the study concept and design; data acquisition, interpretation, and analysis; drafting of the manuscript; and critical revision of the manuscript.
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