Association Between Atrial Fibrillation and Central Sleep Apnea

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Background: We previously described an association between atrial fibrillation and central sleep apnea in a group of patients with congestive heart failure. We hypothesized that the prevalence of atrial fibrillation might also be increased in patients with central sleep apnea in the absence of other cardiac disease.

Methods and Results: We compared the prevalence of atrial fibrillation in a series of 60 consecutive patients with idiopathic central sleep apnea (apnea-hypopnea index > 10 events per hour, > 50% central events) with that in 60 patients with obstructive sleep apnea (apnea-hypopnea index > 10, > 50% obstructive events) and 60 patients without sleep apnea (apnea-hypopnea index < 10), matched for age, sex, and body mass index. Subjects with a history of congestive heart failure, coronary artery disease, or stroke were excluded from the study. The prevalence of atrial fibrillation among patients with idiopathic central sleep apnea was found to be significantly higher than the prevalence among patients with obstructive sleep apnea or no sleep apnea (27%, 1.7%, and 3.3%, respectively, P<.001). However, hypertension was most common and oxygen desaturation most extreme among patients with obstructive sleep apnea.

Conclusions: We conclude that there is a markedly increased prevalence of atrial fibrillation among patients with idiopathic central sleep apnea in the absence of congestive heart failure. Moreover, the high prevalence of atrial fibrillation among patients with idiopathic central sleep apnea is not explainable by the presence of hypertension or nocturnal oxygen desaturation, since both of these were more strongly associated with obstructive sleep apnea.

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INTRODUCTION

ATRIAL FIBRILLATION (AF) IS THE MOST COMMON CHRONIC ARRHYTHMIA IN NORTH AMERICA, AFFECTING 0.4% OF THE GENERAL POPULATION.[1] AMONG patients with congestive heart failure, previous studies have reported a strong association between sleep apnea and AF. In one study, involving 81 patients with congestive heart failure, the prevalence of AF was significantly higher among those with coexisting sleep apnea than in those without sleep apnea.[2]

However, in that study, the investigators did not determine whether AF was linked to sleep apnea in general or to either central or obstructive sleep apnea (CSA and OSA, respectively) in particular. This issue was addressed in another much larger study involving 450 patients with congestive heart failure from our laboratory.[3] In that study, we found a strong association between AF and CSA but not OSA. Among patients with CSA, AF was present in 23%, compared with only 12% in those with OSA, and 7.5% in those with no sleep apnea. Thus, among patients with congestive heart failure, AF is significantly linked to CSA. However, it is not clear whether, in subjects without congestive heart failure, AF is associated with sleep apnea and, if so, what type.

In the general population, OSA is common: its prevalence is approximately 4% to 9% of adults.[4] OSA is associated with a number of cardiovascular disorders,[5] including hypertension,[6] congestive heart failure,[7]and cardiac arrhythmias.[8,9] Some recent reports have suggested that OSA may specifically predispose to AF,[10,11] while at least one study has failed to find such a link.[12] The largest study to date examining this issue[13] found a strong association between AF and OSA, but the diagnosis of OSA was determined through the Berlin Questionnaire in the majority of subjects, rather than the gold standard, full polysomnographic study. Therefore, the prevalence of CSA could not be assessed.

In contrast to OSA, CSA is very uncommon in the general population,[4] and any potential link between CSA and AF has not been examined. In view of our previous finding of an increased prevalence of AF in heart failure patients with CSA,[3] we hypothesized that the prevalence of AF would also be increased in association with CSA in patients without congestive heart failure. Accordingly, we compared the prevalence of AF with CSA in patients with idiopathic central sleep apnea, an uncommon disorder characterized by recurrent central apneas during sleep in the absence of ventilatory or heart failure or stroke,[14] to that in patients with either OSA or no sleep-disordered breathing (SDB).

METHODS

Subjects

We identified patients with idiopathic CSA from a sample of 2500 consecutive patients who underwent diagnostic polysomnography at the Toronto Rehabilitation Institute Sleep Research Laboratory between February 1996 and August 2003. The most common reason for referral of these patients to our sleep laboratory was suspicion of SDB due to symptoms of snoring, witnessed apneas, excessive daytime sleepiness, or insomnia. The criteria for diagnosis of idiopathic CSA were (1) more than 10 apneas and hypopneas per hour of sleep, of which more than 50% were central in nature; (2) no history, signs, or symptoms of congestive heart failure or coronary artery disease; and (3) no history of previous stroke or other neurologic disease. Sixty of the 2500

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patients (2.4%) met the criteria for idiopathic CSA. To determine whether there was a significant relationship between idiopathic CSA and AF, we assembled two control groups: one consisting of 60 subjects with OSA and another consisting of 60 subjects with no SDB. OSA was defined as more than 10 apneas and hypopneas per hour of sleep, of which more than 50% were obstructive in nature, whereas no SDB was defined as fewer than 10 apneas and hypopneas per hour of sleep. Control groups were assembled by reviewing consecutive patients and searching for those with OSA or no SDB, starting with patients studied in February 2002 and going back in time (until December 2000 for the OSA group and July 2000 for the no SDB group) until a group of 60 patients matched for age, sex, and body mass index to the group with idiopathic CSA was identified. Matching was performed by two investigators who were blinded to the presence of atrial fibrillation. AF was identified in all three groups by examination of the single-lead electrocardiogram obtained during the night of the study. In all cases in which AF was identified, the rhythm was present during the entire night. As for the subjects with idiopathic CSA, patients with a history of congestive heart failure, coronary artery disease, or stroke were excluded from the control groups.

Sleep Studies

Overnight polysomnography was performed in all subjects with scoring of sleep stages and movement arousals and measurement of tidal volume and mean oxyhemoglobin saturation (SaO_2) using standard techniques and equipment.[15] Apneas and hypopneas were identified by a calibrated respiratory inductance plethysmograph according to the recommendations of the American Academy of Sleep Medicine.[16] Central apneas were defined by the absence of a tidal volume excursion for at least 10 seconds, whereas hypopneas were defined as a 50% or greater reduction in tidal volume from the baseline value, with in-phase movements of the rib cage and abdominal channels, for at least 10 seconds. Obstructive apneas and hypopneas were defined similarly, except that out-of-phase motion of the rib cage and abdomen had to be present during the event. To enhance comparability of our findings with those reported previously in the literature,[2,3] we used an apnea-hypopnea index (AHI) of more than 10 per hour to indicate the presence of sleep apnea for our analysis.

Assessment of Cardiac Function

To determine whether there was evidence of significant left ventricular (LV) systolic dysfunction in our patients with idiopathic CSA and AF, we examined the duration of their central apnea-hyperpnea cycles. We have previously shown that this cycle duration in patients with CSA is inversely proportional to cardiac output and is much shorter in patients with idiopathic CSA and normal LV function than it is in patients with CSA and depressed LV systolic dysfunction.[17] Cycle duration was measured as the time from apnea onset to the subsequent apnea onset, and we averaged 5 consecutive cycles during the first episode of stage 2 sleep to obtain a mean cycle duration. Echocardiographic assessments were performed in 14 of our 16 patients with AF and idiopathic CSA within 3 months of their sleep studies to quantify LV systolic function. These assessments were performed and interpreted by personnel without knowledge of the sleep-study findings. LV function was classified as normal (grade 1: LV ejection fraction [LVEF] ≥60%), mildly impaired (grade 2: LVEF 40 to <60%), moderately impaired (grade 3: LVEF 20 to <40%), and severely impaired (grade 4: LVEF <20%).

Table 1—Patient Characteristics

	Idiopathic CSA	OSA	No SDB
Age, y	56.8 ± 15.8	56.6 ± 12.4	54.6 ± 14.1
Men:women	51:9	51:9	51:9
Body mass index, kg/m^2	29.2 ± 4.5	30.0 ± 4.5	28.1 ± 4.1
SaO_2 minimum, % [range]	88.1 [85.1, 90.6]	85.1 [79.5, 89.3]*	89.1 [86.6, 91.6]
AHI, events/h			
Total	30.4 ± 17.7	30.3 ± 16.8	5.5 ± 2.7
Central	23.1 ± 14.7	2.5 ± 3.5	3.6 ± 3.0
Obstructive	7.2 ± 7.7	27.8 ± 16.5	1.9 ± 2.7
Atrial fibrillation, no. (%)	16 (27)†	1 (1.7)	2 (3.3)
Hypertension, no. (%)	17 (28)	30 (50)*	14 (23)

Data are presented as mean ± SD unless otherwise specified.
AHI refers to apnea-hypopnea index; SaO_2, oxyhemoglobin saturation.
*P < .05 compared with idiopathic central sleep apnea (CSA) and no sleep-disordered breathing (SDB) groups.
†P < .001 compared with obstructive sleep apnea (OSA) and no-SDB groups.

Statistical Analyses

Comparisons of continuous variables among the groups were made with 1-way analysis of variance in the case of normally distributed data and Kruskal-Wallis 1-way analysis of variance on ranks if the data were not normally distributed, followed by subsequent pairwise comparisons using the Tukey Test or Dunn Method, respectively. Categorical variables were compared by the χ^2 test. The statistical software used was Sigmastat 2.03 (SPSS, Inc., Chicago, IL). Results were considered significant if $P < .05$.

RESULTS

Subjects in the OSA and no sleep apnea control groups were well matched to the idiopathic CSA group for age, sex distribution, and body mass index (Table). By design, the AHI was greater in the idiopathic CSA and OSA groups than in the no-SDB group, while the AHI was similar between the idiopathic CSA and OSA groups. Among patients with idiopathic CSA, 76% of their apneas and hypopneas were central in nature, while in patients with OSA, 92% were obstructive. If we confined our analysis to apneas only, 83% of apneas were central in our patients with idiopathic CSA, and 82% of apneas were obstructive in the group with OSA. This indicated that scoring of hypopneas closely reflected scoring of apneas and strongly suggested that the classification of hypopneas was accurate. Therefore, the proportion of central versus obstructive events in the idiopathic CSA and OSA groups were widely separated. Minimum SaO_2 was significantly lower in the OSA group than in either of the other 2 groups. However, minimum SaO_2 in the idiopathic CSA and no-SDB groups did not differ significantly.

The prevalence of AF in patients with idiopathic CSA (27%)

was 16-fold higher than in the OSA group (1.7%) and 8-fold higher than in the no-SDB group (3.3%). (P<.001). The prevalence of AF among patients with OSA was not significantly different from those without sleep apnea. In contrast, the prevalence of hypertension and the severity of nocturnal O_2 desaturation were both greatest among patients with OSA.

The mean apnea-hyperpnea cycle duration of the 60 patients with idiopathic CSA in the present study was 41±12 seconds, which is in keeping with the short cycle duration of 37±3 seconds previously reported in patients with idiopathic CSA. It was much shorter than the mean 59±5-second cycle duration observed in congestive heart failure patients with depressed LV systolic function.[17] Among the 14 idiopathic CSA patients with AF who had echocardiographic assessments of LVEF, 12 had normal LV systolic function (grade 1; LVEF ≥60%) and only 2 had very mild LV systolic dysfunction (grade 2; LVEF 40%-60%).

DISCUSSION

The novel finding of our study is that patients with idiopathic CSA have a much higher prevalence of AF than do patients with OSA or no sleep apnea. Our findings are consistent with our previous study that demonstrated a strong association between CSA and AF among patients with congestive heart failure.[3] However, the present findings extend those results by demonstrating that the strong association between CSA and AF is not confined to patients with congestive heart failure, but also occurs in its absence.

The relationship between AF and idiopathic CSA may be explainable by 3 nonmutually exclusive possibilities: (1) AF predisposes to idiopathic CSA, (2) idiopathic CSA predisposes to AF or (3) both idiopathic CSA and AF are brought about secondary to an unidentified underlying abnormality of central cardiorespiratory regulation.

AF might lead to CSA through a mechanism similar to that associated with congestive heart failure. Because AF leads to decreased pumping efficiency of the heart, cardiac output is lowered, and pulmonary vascular pressures are raised. Raised pulmonary vascular pressures can trigger hyperventilation and hypocapnia through stimulation of pulmonary vagal irritant receptors.[18-20] Hypocapnia, especially in concert with a lowered cardiac output, predisposes to respiratory system instability and CSA.[5,21] The implication that AF might lead to CSA is of particular interest, given recent reports describing the usefulness of atrial overdrive pacing in the treatment of sleep apnea.[22]

Alternatively, idiopathic CSA may predispose to AF in some patients. Patients with idiopathic CSA chronically hyperventilate while awake and asleep, leading to respiratory control system instability.[23,24] The resulting hypocapnia might influence transmembrane currents and thus impair cardiac electrical stability.[25] In contrast, hypoxia is unlikely to be playing a major role in triggering AF, since apnea-related hypoxia is less pronounced in CSA than in OSA (Table). Neither can exaggerated negative intrathoracic pressure during apneas and hypopneas, which is present in OSA but absent in CSA, be contributing to the pathogenesis of AF in idiopathic CSA. It is also important to note that hypertension, which predisposes to AF,[1] was also more common among OSA patients and, thus, not responsible for the high prevalence of AF in patients with idiopathic CSA.

Finally, both AF and CSA might result from a shared, underlying, predisposing factor. Patients with idiopathic CSA have increased central and peripheral chemoresponsiveness,[26] a trait they share with congestive heart failure patients with CSA.[19,21] In the case of patients with heart failure, one factor that is thought to contribute to this enhanced chemoresponsiveness is increased sympathetic activity, which can potentiate peripheral chemoreceptor sensitivity.[27-29] While there is no direct evidence available, it is possible that the increased chemoresponsiveness observed in patients with idiopathic CSA is at least in part related to an underlying abnormality of the central sympathetic nervous system that might also predispose to the development of AF.[30]

In contrast to our results in patients with idiopathic CSA, we did not find an increased prevalence of AF among patients with OSA, a finding that is in agreement both with our previous study in heart failure patients[3] and that of Porthan et al.[12] Our findings are in contrast to those of a recent study examining this issue,[13] which found a strong association between AF and OSA. However, in that study, the diagnosis of OSA was determined mainly through the Berlin Questionnaire, rather than the gold standard—full polysomnographic study. The Berlin Questionnaire has acceptable sensitivity and specificity for the diagnosis of OSA in a primary care setting but would be expected to have worse specificity among patients with cardiac disease, many of whom may have disturbed sleep and daytime fatigue for reasons other than sleep apnea. More importantly, the Berlin Questionnaire cannot distinguish CSA from OSA.

One limitation of our study is the potential for a bias resulting from a change in referral patterns. Patients in our control groups were referred more recently on average than were the patients with idiopathic CSA. However, we do not believe this is likely to explain our findings, since interest in SDB as a contributor to AF has been increasing in recent years, and any temporal effect would thus be biased in favor of a higher prevalence of AF in the control groups. Nonetheless, we cannot completely exclude the possibility of a temporal referral bias.

In conclusion, the present study is the first to demonstrate a relationship between AF and CSA in the absence of congestive heart failure. While the pathophysiologic mechanisms underlying this relationship remain to be determined, our results complement recent reports suggesting that cardiac overdrive pacing may improve CSA in patients with bradyarrhythmias,[22] many of whom had AF. While CSA apnea is known to be associated with increased mortality in the setting of heart failure,[31] it remains to be elucidated whether CSA associated with AF has the same adverse implications. Further studies will be needed to clarify this issue.

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