Central Sleep-disordered Breathing Predicts Incident Atrial Fibrillation in Older Men

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Abstract

Rationale: Although research supports a sleep-disordered breathing and atrial fibrillation association, prospective data examining sleep-disordered breathing predicting incident atrial fibrillation are lacking.

Objectives: To investigate sleep-disordered breathing indices as predictors of incident atrial fibrillation.

Methods: A cohort (n = 843) of ambulatory older men without prevalent atrial fibrillation was assessed for baseline sleep indices: apnea-hypopnea index, central sleep apnea (central apnea index, ≥ 5 vs. < 5), central sleep apnea or Cheyne-Stokes respiration, obstructive apnea-hypopnea index, and percentage of sleep time with less than 90% oxygen saturation. Incident clinically symptomatic adjudicated or self-reported atrial fibrillation outcome was ascertained (mean follow-up, 6.5 ± 0.7 yr). We used logistic regression models adjusted for age, race, body mass index, cardiopulmonary disease, alcohol use, pacemaker, cholesterol, cardiac medications, and alternate apnea type for obstructive and central apnea. Age interaction terms and median age-stratified analyses were performed.

Measurements and Main Results: Central sleep apnea (odds ratio [OR], 2.58; 95% confidence interval [CI], 1.18–5.66) and Cheyne-Stokes respiration with central sleep apnea (OR, 2.27; 95% CI, 1.13–4.56), but not obstructive apnea or hypoxemia, predicted incident atrial fibrillation. Central apnea, Cheyne-Stokes respiration, and sleep-disordered breathing-age interaction terms were significant ($P < 0.05$). Unlike the case with younger participants, among participants aged 76 years or older (albeit with small atrial fibrillation counts), atrial fibrillation was related to central apnea (OR, 9.97; 95% CI, 2.72–36.50), Cheyne-Stokes respiration with central apnea (OR, 6.31; 95% CI, 1.94–20.51), and apnea-hypopnea index (OR, 1.22; 95% CI, 1.08–1.39 [per 5-unit increase]).

Conclusions: In older men, central apnea and Cheyne-Stokes respiration predicted increased atrial fibrillation risk, with findings being strongest in older participants in whom overall sleep-disordered breathing also increased atrial fibrillation risk.

Keywords: atrial fibrillation; cohort study; sleep-disordered breathing

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At a Glance Commentary

Scientific Knowledge on the

Subject: Obstructive sleep apnea has been linked with atrial fibrillation (AF) in clinic-based, cross-sectional, and retrospective studies.

What This Study Adds to the

Field: In a large, population-based, multicenter, prospective study with careful collection of sleep measures involving a cohort of older men vulnerable to AF development, central sleep apnea and Cheyne-Stokes respiration were associated with incident AF. In the older (age ≥ 76 yr) but not the younger subgroup, all sleep-disordered breathing indices, including both obstructive and central measures, were associated with incident AF.

Sleep-disordered breathing (SDB) is a highly prevalent physiologic stressor that has been implicated in the burden of atrial fibrillation (AF) (1–3). SDB is characterized by repetitive breathing cessation accompanied by physiologic stressors that include intermittent hypoxia, hypercapnia, autonomic nervous system fluctuations, and intrathoracic pressure swings, which can predispose individuals to enhanced arrhythmogenicity. AF is highly prevalent, particularly with increasing age, as evidenced by a threefold increase between the sixth and eighth decades of life (4). The large population burden of AF is highlighted by a progressively increased prevalence, estimated to reach 10 million in the United States by 2050, and contributes to substantial health care costs and morbidity (4–7).

Cross-sectional epidemiologic data have identified a strong association between AF and SDB (8, 9). The plausibility of a causal relationship is supported by data from a case-crossover study that identified an increase in paroxysmal AF events immediately following SDB events, suggesting that respiratory disturbances may trigger AF events (10). However, an important limitation of existing community-based epidemiologic studies is their cross-sectional nature, which precludes understanding of the temporal relationship between exposure (SDB and its

subtypes) and outcome (AF), thereby limiting ability to inform causality (8, 9). In large, retrospective, clinic-based studies with a focus on obstructive sleep apnea (OSA), researchers have identified (1) an association of nocturnal oxygen desaturation and incident AF only in participants younger than 65 years of age (11) and (2) a dose–response relationship of OSA severity and hypoxemia with incident AF (12). Existing data also suggest that central events may more significantly associate with atrial arrhythmogenesis, while obstructive respiratory events may more strongly contribute to ventricular arrhythmogenesis (9). Although rigorously conducted randomized controlled trials are lacking, data from retrospective studies identify the impact of primarily OSA (but not central sleep apnea [CSA]) treatment on reduction of the recurrence of AF after cardioversion or ablation, and they allude to a potential causal relationship (13–17).

Although existing studies support an association of SDB and AF, it remains unclear whether SDB serves as a causal risk factor in the development of AF or vice versa. Gaining insight into the role of initiators of AF such as SDB is key to the development of AF prevention strategies and has been identified as a critical knowledge gap by several national AF prevention and treatment expert working groups (18, 19). Furthermore, understanding the SDB characteristics (i.e., obstructive, central, and hypoxemic) that contribute to atrial arrhythmogenesis may allow honing of prevention and treatment to target the specific physiologic determinants of abnormal sleep-related breathing that lead to AF development.

To further characterize the relationship of SDB and its subtypes with AF, we examined SDB and AF development in a prospective, large-scale, multicenter, community-based study of older men, a group particularly vulnerable to AF and its morbidity. To do so, we systematically collected polysomnography (PSG) data and used standardized methods of clinically symptomatic AF identification, and we also analyzed self-reported AF data (20). We hypothesized that SDB would predict incident AF and postulated that central apnea would represent the strongest SDB determinant of predicting future AF (8, 11). Some of the results of these studies were

reported previously in the form of an abstract (21).

Methods

Participants and Study Design

This prospective observational study involved participants in the MrOS Sleep (Outcomes of Sleep Disorders in Older Men) Study, an ancillary study of the MrOS (Osteoporotic Fractures in Men) Study. The MrOS investigators enrolled 5,994 community-living men aged 65 years and older who were able to ambulate without assistance and were without a history of bilateral hip replacement. They recruited participants at six centers (Birmingham, AL; Minneapolis, MN; the Monongahela Valley, near Pittsburgh, PA; Palo Alto, CA; Portland, OR; and San Diego, CA) (22, 23). The MrOS study design, methods, and demographics were published previously (*see online supplement*) (9, 22, 23).

The MrOS Sleep Study researchers recruited 3,135 participants between December 2003 and March 2005 for a comprehensive sleep assessment. Of the 3,135 MrOS Sleep Study participants recruited, 179 did not participate in PSG secondary to refusal or contemporaneous treatment for SDB, and 45 men had failed sleep studies (1.5%), thus leaving 2,911 participants. Of these, 2,316 did not have PSG-identified or self-reported prevalent AF at the first sleep visit. A subgroup of men ($n = 852$) participated in a second sleep visit between November 2009 and March 2012. The analytic cohort consisted of study participants with acceptable PSG at the initial sleep visit, data on incident adjudicated and self-reported AF ($n = 843$), and mean follow-up time of 6.5 ± 0.7 years (Figure 1). Additional recruitment information is provided in the online supplement.

Each site and the study coordinating center received ethical approval from their institutional review boards. Written informed consent was obtained from all participants.

PSG Data

Unattended home PSG (Safiro ambulatory EEG system; Compumedics, Abbotsford, Australia) was performed. It consisted of recording of C3/A2 and C4/A1 electroencephalograms, bilateral

electrooculograms, a bipolar submental electromyogram, thoracic and abdominal inductance plethysmography, airflow (oronasal thermocouple and nasal pressure cannula), finger pulse oximetry, lead I ECG, body positions, and bilateral leg movements (9). Indices per hour of sleep included the apnea–hypopnea index (AHI; measure of the number of obstructive and central apneas and hypopneas with $\geq 3\%$ oxygen desaturation) (24), obstructive apnea–hypopnea index (OAHI; measure of the number of obstructive apneas and hypopneas with $\geq 3\%$ desaturation), and central apnea index (CAI; measure of the number of central apneas). Cheyne–Stokes respiration (CSR) was characterized by a minimum consecutive 10-minute period of a crescendo–decrescendo respiratory pattern culminating in a nadir of central apneas with typical cycle length. The percentage of total sleep time (TST) spent below an oxygen saturation of 90% defined sleep-related hypoxemia.

Outcome Measures

AF was defined as either incident adjudicated AF or self-reported AF (25–27).

Adjudicated clinically symptomatic AF—defined by symptoms, hospitalization, prolongation of hospitalization, or requiring invasive procedure—was identified by surveying for incident events followed by central adjudication using a standard protocol (*see* online supplement). Self-reported AF was ascertained at each sleep visit by asking participants if they had ever been diagnosed with AF or atrial flutter.

Covariate Measures

Covariate measures, including demographics, medical history, alcohol use, cardiovascular disease (CVD) medications (calcium channel blockers, nonophthalmic β -blockers, cardiac glycosides, or antiarrhythmic medications such as cardiac sodium channel blockers and potassium channel blockers), body mass index (BMI), cholesterol level, and pacemaker presence were assessed (28). CVD was defined by history of myocardial infarction, angina, angioplasty, congestive heart failure (CHF), and/or coronary artery bypass graft surgery. A full description of covariate

collection is provided in the online supplement.

Statistical Analysis

PSG parameters were expressed as continuous and/or categorical variables, the latter informed by standard cutoffs (29) or distributional characteristics. SDB was defined per 5-unit AHI increase and alternatively as AHI greater than or equal to 15 versus less than 15 based upon clinical convention (29) and as OSA per 5-unit OAHI increase. CSA was defined as CAI of 5 or greater versus CAI less than 5 and CSA–CSR as CAI of 5 or greater or CSR. TST spent below an oxygen saturation of 90% was defined per category, given its skewed nature ($<1\%$, 1 to $<3.5\%$, 3.5 to $<10\%$, and $\geq 10\%$).

Participant characteristics were summarized as mean $\pm$ SD or count and percentage, and they were compared by AHI category using χ^2 tests for categorical variables, t tests for normally distributed continuous variables, and Wilcoxon rank-sum tests for continuous variables with skewed distributions. SDB or nocturnal hypoxemia and subsequent AF risk associations were assessed by logistic regression. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Models are presented as minimally adjusted (age, clinic, and race) and multivariable adjusted (age; clinic; race; BMI; total cholesterol; self-reported history of CVD, hypertension, diabetes, stroke, alcohol use, and chronic obstructive pulmonary disease; pacemaker placement; use of CVD medications; and OAHI in the CSA and CSA–CSR models and CAI in the OSA model). We assessed SDB by age interaction (significant if $P < 0.10$) and stratified by median age (<76 yr, ≥ 76 yr) (8). Sensitivity analyses included separate analyses excluding participants with a history of CHF or incident CHF.

All significance levels reported are two-sided, and all analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Study Population

Of 843 participants in the final analytic study sample, 86% were white. Their average BMI was 27 ± 4 kg/m². Compared

Figure 1. MrOS (Osteoporotic Fractures in Men) Study design: recruitment, attrition, and retention. PSG = polysomnography.

with those in our analysis subset, the 390 men who died before sleep visit 2 had higher rates of CAI of 5 or greater (6% vs. 8%; $P = 0.13$) and higher rates of CSA-CSR (8% vs. 11%; $P = 0.07$), although these differences did not reach statistical significance. As expected for this age range, 45% had hypertension. Although 25% had some form of CVD, only 3% of participants had a self-reported history of heart failure (Table 1). Compared with those with AHI less than 15, those with AHI of 15 or greater (42% of participants) had a significantly higher BMI, more prevalent hypertension, and a higher percentage of TST with hypoxemia (Table 1). Compared with the 843 men in our analytic cohort, the 1,473 men with PSG data without a history of AF who did not participate in the second examination were similar, on average, in SDB indices and BMI and had similar rates of chronic obstructive lung disease, stroke, diabetes, and pacemaker placement

($P > 0.05$). However, these men were older by 2.5 years, on average, and had a higher percentage of hypertension, CVD, CHF, and cardiac medication use as well as lower alcohol intake ($P < 0.05$).

Sleep-disordered Breathing Indices and Incidence of Atrial Fibrillation

There were 99 cases of AF (12%) reported during the follow-up period. SDB variables were analyzed in relation to AF incidence (Table 2). Overall, SDB defined by AHI level was not a significant predictor of incident AF when considered as a continuous or dichotomous variable. Alternatively, CSA (OR, 2.58; 95% CI, 1.18–5.66) and CSA-CSR (OR, 2.27; 95% CI, 1.13–4.56) were significantly related to incident AF in the multivariable model including heart failure and OSA severity. Hypoxemia, as defined by percentage of TST with saturation less than 90%, was a significant predictor of AF in minimally adjusted analyses

(3.5% to <10% vs. <1%: OR, 1.97; 95% CI, 1.07–3.63) but not in fully adjusted analyses. Indices of OSA were not significantly related to incident AF.

Secondary Analyses

There was a statistically significant interaction of CSA, CSA-CSR, and AHI indices with age for the incident AF outcome ($P < 0.05$). In multivariable adjusted stratified analyses (Table 3), SDB was significantly associated with AF development in men aged 76 years or older. The OR for AHI per 5-unit increase was 1.22 (95% CI, 1.08–1.39), and that for AHI greater than or equal to 15 was 2.64 (95% CI, 1.16–6.00). Similar to the case in primary analyses, CSA indices remained significant predictors of incident AF in adjusted analyses, with an observed stronger magnitude of association. The OR for CAI greater than or equal to 5 was 9.97 (95% CI, 2.72–36.50), and that for CSA-CSR was 6.31 (95% CI, 1.94–20.51); however, this analysis was

Table 1. Baseline Characteristics of Participants

Characteristic	Overall (N = 843)	AHI <15 (n = 491)	AHI ≥15 (n = 352)	P Value
Age, yr	75 ± 5	74 ± 5	75 ± 5	0.50
Race/ethnicity				0.89
White	726 (86)	419 (85)	307 (87)	
African American	36 (4)	22 (5)	14 (4)	
Asian	40 (5)	25 (5)	15 (4)	
Other	41 (5)	25 (5)	16 (4)	
Body mass index, kg/m ²	27 ± 4	27 ± 4	28 ± 4	<0.0001
Diabetes	101 (12)	56 (11)	45 (13)	0.54
Hypertension	383 (45)	202 (41)	181 (51)	0.003
Cardiovascular disease*	208 (25)	115 (23)	93 (26)	0.32
Heart failure	25 (3)	12 (2)	13 (4)	0.29
Stroke	22 (3)	16 (3)	6 (2)	0.16
Chronic obstructive pulmonary disease or emphysema	33 (4)	18 (4)	15 (4)	0.66
Pacemaker placement	17 (2)	8 (2)	9 (3)	0.34
Total cholesterol, mg/dl	197 ± 34	196 ± 33	198 ± 36	0.45
Taking cardiovascular medications	272 (32)	150 (31)	122 (35)	0.21
Alcohol use, drinks/wk				0.61
<1	384 (46)	229 (47)	155 (44)	
1–13	393 (47)	226 (46)	167 (48)	
≥14	60 (7)	32 (7)	28 (8)	
Obstructive apnea–hypopnea index	16 ± 14	7 ± 4	29 ± 13	<0.0001
Central apnea index ≥5	48 (6)	4 (1)	44 (13)	<0.0001
Cheyne-Stokes respiration with central sleep apnea	68 (8)	12 (2)	56 (16)	<0.0001
Percentage of total sleep time with SaO ₂ <90%				<0.0001
<1%	416 (49)	339 (69)	77 (22)	
1 to <3.5%	236 (28)	108 (22)	128 (36)	
3.5 to <10%	100 (12)	23 (5)	77 (22)	
≥10%	91 (11)	21 (4)	70 (20)	

Definition of abbreviation: AHI = apnea–hypopnea index.

For continuous variables, means and SDs are presented; for categorical variables, number and percentage are given. P values were generated from t tests for normally distributed continuous variables, Wilcoxon rank-sum tests for skewed variables, and χ^2 tests for categorical data.

*Cardiovascular disease includes myocardial infarction, angina, heart failure, coronary bypass surgery, and angioplasty.

Table 2. Adjusted Associations of Sleep-disordered Breathing Predictors and Incident Atrial Fibrillation or Flutter

Predictor	Events/Total	Minimally Adjusted OR* (95% CI)	Multivariable Adjusted OR† (95% CI)
AHI per 5-unit increase	99/843	1.05 (0.98–1.13)	1.01 (0.94–1.10)
AHI <15	49/491	1.00 (reference)	1.00 (reference)
AHI ≥15	50/352	1.47 (0.95–2.27)	1.15 (0.72–1.84)
OAH per 5-unit increase‡	99/843	1.04 (0.97–1.12)	0.98 (0.91–1.07)
CAI <5	88/795	1.00 (reference)	1.00 (reference)
CAI ≥5‡	11/48	2.34 (1.14–4.77)	2.58 (1.18–5.66)
No CSA-CSR	85/775	1.00 (reference)	1.00 (reference)
CSA-CSR‡	14/68	2.10 (1.11–3.97)	2.27 (1.13–4.56)
Percentage of total sleep time with SaO ₂ <90%			
<1%	43/416	1.00 (reference)	1.00 (reference)
1% to <3.5%	24/236	0.93 (0.55–1.60)	0.83 (0.47–1.47)
3.5% to <10%	19/100	1.97 (1.07–3.63)	1.64 (0.83–3.24)
≥10%	13/91	1.31 (0.65–2.64)	1.01 (0.46–2.24)

Definition of abbreviations: AHI = apnea–hypopnea index; CAI = central apnea index; CI = confidence interval; CSA-CSR = Cheyne-Stokes respirations or central sleep apnea; OAH = obstructive apnea–hypopnea index; OR = odds ratio.

OAH adjustment is continuous; CAI adjustment is CAI ≥5. Bold denotes statistically significant values.

*Adjusted for age, clinic, and race.

†Adjusted for age, clinic, race, body mass index, history of cardiovascular disease, hypertension, diabetes, stroke, chronic obstructive pulmonary disease, pacemaker placement, total cholesterol, use of cardiovascular medications, and alcohol use.

‡Multivariable models were further adjusted by alternate apnea type: Models with CAI and CSA-CSR predictors were further adjusted by OAH; the model with the OAH predictor was further adjusted by CAI.

hampered by low participant counts in the category for both CAI and CSA-CSR. Although OSA as defined using OAH as a continuous variable was a significant predictor of incident AF in minimally adjusted models, this association lost significance in the fully adjusted model. Consistent with findings from the primary analyses, hypoxemia was not significantly associated with incident AF. After excluding those men who had a history of CHF or who developed CHF during follow-up, the results remained significant in multivariable models for CSA-CSR (OR, 2.56; 95% CI, 1.17–5.58) and were similar in magnitude to and marginally significant for CSA (OR, 2.42; 95% CI, 0.98–5.96) ($P = 0.05$).

Discussion

In this prospective, multicenter study of community-dwelling older men, indices of CSA, including CSR, were significantly associated with incident AF even after accounting for confounders, including cardiovascular risk and disease. Additionally, there was effect modification by age such that all SDB indices were significant predictors of incident AF. Overall, SDB as defined by AHI, as well as central SDB as defined by CSA and CSA-CSR, significantly predicted AF in participants older than the median age

(≥76 yr) even after consideration of cardiopulmonary risk. The robustness of these findings persisted in sensitivity analyses excluding those with self-reported heart failure. Although these prospective findings do not prove a causal relationship of CSA with AF, they highlight the potential role of CSA as a marker of AF development (19).

Our finding of a stronger relationship of central apnea than OSA with AF is consistent with previously published cross-sectional results and identifies CSA as a predictor of AF development (9). Unlike the prior cross-sectional epidemiologic work, AF ascertainment in the present study was based on incident events identified either through adjudication or by self-report and not exclusively based on AF identified by ECG monitoring during the MrOS Sleep Study. A preponderance of data elucidates specific underlying mechanisms related to SDB that contribute to atrial arrhythmogenicity. Autonomic dysfunction, a well-recognized corollary of SDB characterized by enhanced vagal activity during and sympathetic activation subsequent to the respiratory events, increases the likelihood of AF by shortening the atrial effective refractory period and predisposes individuals to focal atrial firing (“adrenergic AF”), respectively (30, 31). SDB-related intermittent hypoxia represents a potent stimulus of autonomic

function activation that creates regions of heterogeneous myocyte excitability, thereby increasing AF propensity (32). On one hand, substantial negative intrathoracic pressure alterations observed in OSA may lead to an abrupt decrease in left atrial volume and reduction in left ventricular systolic performance, augmenting AF development (33). On the other hand, some data suggest that the reverse may be true (i.e., that AF may lead to SDB). Paroxysms of AF have been described as occurring subsequent to discrete apneic events plausibly due to immediate effects of tachycardia-induced left ventricular dysfunction and diastolic dysfunction, leading to reduction of cardiac output and increased pulmonary vascular pressure and hence resulting in breathing instability (34, 35). The findings of the present study provide further evidence to support the importance of central apnea pathophysiology leading to AF.

Mechanistically, CSA is characterized by ventilatory system instability that results in hypocapnia, which may contribute to cardiac electrical instability (36). An underlying increase in central and peripheral chemoresponsiveness may contribute to augmented sympathetic activity and autonomic imbalance, which are predisposing factors for AF (37–39). It is possible that CSA is a marker of

Table 3. Age-stratified Adjusted Associations of Sleep-disordered Breathing Predictors and Incident Atrial Fibrillation or Flutter

Predictor	Events/Total	Minimally Adjusted OR* (95% CI)	Multivariable Adjusted OR† (95% CI)
Age <76 yr			
AHI per 5-unit increase	57/529	0.95 (0.86–1.06)	0.92 (0.82–1.04)
AHI <15	33/308	1.00 (reference)	1.00 (reference)
AHI ≥15	24/221	0.96 (0.54–1.70)	0.79 (0.42–1.49)
OAHl per 5-unit increase‡	57/529	0.95 (0.85–1.06)	0.92 (0.82–1.04)
CAI <5	53/500	1.00 (reference)	1.00 (reference)
CAI ≥5‡	4/29	1.33 (0.44–3.99)	1.22 (0.34–4.41)
No CSA-CSR	51/486		
CSA-CSR‡	6/43	1.36 (0.55–3.40)	1.45 (0.52–4.07)
Percentage of total sleep time with SaO ₂ <90%			
<1%	29/276	1.00 (reference)	1.00 (reference)
1% to <3.5%	11/139	0.69 (0.33–1.45)	0.61 (0.28–1.35)
3.5% to <10%	12/61	2.13 (0.99–4.57)	1.74 (0.71–4.24)
≥10%	5/53	0.78 (0.27–2.23)	0.57 (0.18–1.82)
Age ≥76 yr			
AHI per 5-unit increase	42/314	1.20 (1.08–1.33)	1.22 (1.08–1.39)
AHI <15	16/183	1.00 (reference)	1.00 (reference)
AHI ≥15	26/131	2.91 (1.43–5.90)	2.64 (1.16–6.00)
OAHl per 5-unit increase‡	42/314	1.17 (1.05–1.30)	1.13 (0.98–1.29)
CAI <5	35/295	1.00 (reference)	1.00 (reference)
CAI ≥5‡	7/19	4.86 (1.72–13.72)	9.97 (2.72–36.50)
No CSA-CSR	34/289	1.00 (reference)	1.00 (reference)
CSA-CSR‡	8/25	3.88 (1.50–10.07)	6.31 (1.94–20.51)
Percentage of total sleep time with SaO ₂ <90%			
<1%	14/140	1.00 (reference)	1.00 (reference)
1% to <3.5%	13/97	1.34 (0.58–3.09)	1.69 (0.65–4.40)
3.5% to <10%	7/39	1.93 (0.67–5.51)	2.24 (0.69–7.30)
≥10%	8/38	2.38 (0.87–6.52)	2.68 (0.77–9.34)

For definition of abbreviations, see Table 2.

The *P* value for interaction was significant for all variables (*P* < 0.10). Interactions with age as a categorical variable (above or below median): AHI continuous, *P* = 0.01; AHI ≥15, *P* = 0.04; OAHl, *P* = 0.02. Interactions of age as a continuous variable: CAI ≥5, *P* = 0.04; CSA-CSR, *P* = 0.02; percentage of total sleep time with SaO₂ <90%, *P* = 0.08. Bold denotes statistically significant values.

*Adjusted for age, clinic, and race.

†Adjusted for age, clinic, race, body mass index, history of cardiovascular disease, hypertension, diabetes, stroke, chronic obstructive pulmonary disease, pacemaker placement, total cholesterol, use of cardiovascular medications, and alcohol use.

‡Multivariable models were further adjusted by alternate apnea type: Models with CAI and CSA-CSR predictors were further adjusted by OAHl; the model with the OAHl predictor was further adjusted by CAI.

augmented respiratory chemoreflexes and autonomic nervous system dysfunction rather than the primary impetus for AF development. However, heart failure is associated with autonomic dysfunction and altered chemosensitivity, so the causal directionality of these associations is unclear (40). Furthermore, as chemoresponsiveness wanes with age, the extent of its role in AF in older patients is unclear (41). Our observation of a relationship of CSA and AF independent of heart failure is corroborated by findings from clinical studies in which researchers reported increased AF in those with central apnea compared with obstructive apnea, even in the absence of heart failure (42). Previous work suggesting that central apnea events directly trigger AF paroxysms also supports a role for CSA in AF development (34). Further evidence implicating CSA as

a true pathogenic factor and not simply a marker of underlying cardiac dysfunction is provided by improvement in heart transplant-free survival in heart failure patients whose CSA was effectively suppressed with positive airway pressure treatment (43). These benefits did not appear to be due to direct positive airway pressure-related improvement in hemodynamics, but rather seemed to result from the reversal of central apnea pathophysiology (i.e., sympathetic nervous system activation secondary to apnea and arousal from sleep) (43, 44). We recognize, however, that we cannot definitively exclude the possibility that CSA may represent a marker of heart disease leading to AF (40, 45). Recent data demonstrate increased mortality in reduced ejection fraction heart failure with CSA treatment by adaptive servoventilation, an advanced

positive airway pressure modality (46). However, given the contrasting pathophysiologic states of heart failure and AF, implications of the reversal of CSA and associated hypoxia and/or sympathetic activation via positive pressure or nonpositive pressure modalities in AF remain unclear and warrant further investigation.

In the present study, stronger associations of SDB with AF were observed in the older study participants. This contrasts with several prior epidemiologic studies demonstrating weaker associations of adverse cardiac outcomes and SDB in older than in younger individuals (8, 11). Differences among studies with regard to age modification are related to differences in age ranges compared. In the present study, the older cohort had a mean age of 76 years, a group in which

the effects of advanced age and SDB may be multiplicative. For example, the pathophysiologic insults of SDB, including intermittent hypoxia, autonomic imbalance, and intrathoracic pressure swings, may have more pronounced effects on atrial arrhythmogenesis when superimposed on the aged heart, which has an electrophysiologic substrate different from that of younger individuals (47–51). Enhanced impulse generation due to increased automaticity, triggered activity, and reentrant circuits within the atria and pulmonary veins are considered to be responsible for AF initiation and maintenance in the elderly and at a specific age threshold may be more likely to occur as a pathophysiologic response to SDB-induced physiologic stress (48, 50, 52).

Unlike prior studies, this work does not show an association with OSA, except in the oldest of the old subgroup. This difference may be secondary to different susceptibilities in the very aged (mean age, 75 yr) compared with those in cohorts that include significant numbers of middle-aged adults (mean age, 49 yr) (11).

This study does not show a relationship between hypoxemia and AF development, a finding that was somewhat unanticipated. A large, single-center, clinic-based study showed that degree of hypoxemia was associated in fully adjusted models with development of AF in individuals younger than 65 years of age but not in those aged 65 years or older (11). Another retrospective cohort study (mean age, 59 yr) affirmed a link between incident AF and hypoxemia but did not find effect modification by age (12). In our cohort (all aged >65 yr), even the younger subgroup did not show a statistically significant relationship of hypoxemia with the development of AF. This may be secondary to different mechanisms of AF development in the elderly compared with younger individuals and may potentially be due to limited power, as an association of hypoxemia and AF was observed in minimally but not fully adjusted models.

Strengths of this study include the prospective design and high rate of follow-up completers (99% for the adjudicated AF). Standardized protocols and procedures were used to maximize data integrity. A systematic consideration of

several metrics of SDB, including central apnea and overnight hypoxemia, was conducted. Limitations of this study include possible residual confounding. Potentially representing overestimates of true risk, small AF event counts in age-stratified analyses led to large CIs, which may be secondary to small differences in AF incidence. A potential limitation is survivorship bias, given the higher prevalence of central SDB in the subset who died ($n = 390$) and did not participate in the second examination; however, exclusion of these participants would be expected to bias the results toward the null. Because this study focused on a cohort of community-dwelling elderly men, the findings may not be generalizable to younger individuals or to women. Measures of cardiac function such as echocardiography were not included, which precludes examination of cardiac function mediation of SDB and AF relationships. Use of self-reported measures of cardiac comorbidity, including heart failure, limited our ability to adjust for potential confounding related to undiagnosed heart disease. Interestingly, the overall higher percentage of participants with CSA-CSR relative to the percentage of participants with self-reported heart failure or stroke suggests the possibility of underreporting of these comorbidities versus central apnea physiology, which is idiopathic or attributable to other factors. In future investigations focused on the underlying pathways that link SDB and AF, researchers should examine the role of cardiac function and structure through morphologic analysis, the interplay between CSA and respiratory chemoreflexes and autonomic dysfunction, and the role of biochemical mediators (i.e., systemic inflammation and oxidative stress). In addition, further characterization of phenotypes of CSA by analysis of apnea, ventilation, and overall cycle length may provide further insight into the mechanism of this phenomenon (53, 54). Although we cannot exclude the possibility that CSA represents a marker of altered chemosensitivity and autonomic dysfunction mediating AF risk, these findings provide a basis on which to stratify risk and target individuals with CSA for AF risk reduction, and they potentially support investigation of CSA pathophysiologic reversal on AF development.

This study highlights the importance of CSA and CSR in the development of incident AF, with results strengthened in the older subgroup of an elderly cohort of men. These findings suggest that CSA serves as an important potential prevention and therapeutic target for AF, particularly in older individuals, the latter representing a group particularly susceptible to AF development and accompanying morbidity. ■

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