Sleep-disordered Breathing and Incident Heart Failure in Older Men

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Abstract

Rationale: The directionality of the relationship between sleep-disordered breathing and heart failure is controversial.

Objectives: We assessed whether elevations in the obstructive or central sleep apnea index or the presence of Cheyne-Stokes breathing are associated with decompensated and/or incident heart failure.

Methods: We conducted a prospective, longitudinal study of 2,865 participants derived from the Osteoporotic Fractures in Men Study, a prospective multicenter observational study of community-dwelling older men. Participants underwent baseline polysomnography and were followed for a mean 7.3 years for development of incident or decompensated heart failure. Our main exposures were the obstructive apnea-hypopnea index (AHI), central apnea index (CAI ≥ 5), and Cheyne-Stokes breathing. Covariates included age, race, clinic site, comorbidities, physical activity, and alcohol and tobacco use.

Measurements and Main Results: CAI greater than or equal to five and presence of Cheyne-Stokes breathing but not obstructive AHI were significant predictors of incident heart failure (adjusted hazard ratio [HR], 1.79; 95% confidence interval [CI], 1.16–2.77 for CAI ≥ 5) (HR, 2.23; 95% CI, 1.45–3.43 for Cheyne-Stokes breathing). After excluding those with baseline heart failure, the incident risk of heart failure was attenuated for those with CAI greater than or equal to five (HR, 1.57; 95% CI, 0.92–2.66) but remained significantly elevated for those with Cheyne-Stokes breathing (HR, 1.90; 95% CI, 1.10–3.30).

Conclusions: An elevated CAI/Cheyne-Stokes breathing, but not an elevated obstructive AHI, is significantly associated with increased risk of decompensated heart failure and/or development of clinical heart failure in a community-based cohort of older men.

Keywords: sleep apnea; Cheyne-Stokes breathing; heart failure; epidemiology

Heart failure (HF) is a common condition in older adults and is associated with significant morbidity, mortality, and cost (1, 2). An estimated 5.1 million people in the United States have HF, and about half of those diagnosed with HF will die within 5 years (2). The United States spends approximately \$32 billion per year because

of the health care costs, medications, and decreased function resulting from this disease (1). There is a high prevalence of sleep apnea (SA) in individuals with HF (3–5) and presence of comorbid SA is associated with lower ejection fraction, higher New York Heart Association class, and increased overall morbidity and

mortality (6, 7). Furthermore, effective treatment of SA in individuals with comorbid HF has been reported to result in decreased morbidity and improved survival (7–9).

SA can be classified into obstructive SA (OSA) or central SA (CSA) with or without Cheyne-Stokes breathing (CSB). OSA is

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At a Glance Commentary

Scientific Knowledge on the

Subject: Sleep-disordered breathing and heart failure are highly prevalent comorbid conditions, and evidence demonstrates increased morbidity and adverse outcomes in patients with heart failure with comorbid sleep apnea. However, it is unclear whether sleep apnea is an antecedent risk factor for clinical heart failure. Furthermore, the degree to which obstructive versus central sleep apnea modulates the natural history of ventricular dysfunction is also unclear.

What This Study Adds to the

Field: This study is the first to demonstrate that older men with an elevated central sleep apnea index or Cheyne-Stokes breathing, but not an elevated obstructive sleep apnea index, are at significantly increased risk of heart failure decompensation. Men with Cheyne-Stokes breathing also are at risk for incident heart failure. These data suggest that central sleep apnea/Cheyne-Stokes breathing is not simply a marker of more severe heart failure but may precede the onset of clinical heart failure, making those with subclinical ventricular dysfunction more likely to decompensate. These results suggest that screening individuals with an elevated central sleep apnea index or Cheyne-Stokes breathing for occult heart failure may be important and that providing effective treatment of their sleep-disordered breathing may mitigate this risk.

characterized by hypopneas (reduction in breathing coupled with ≥ 3 –4% desaturations) and apneas (cessation of breathing for at least 10 s) despite persistent respiratory effort. CSA is characterized by apneas and hypopneas in the absence of inspiratory effort and CSB by cycles of crescendo–decrescendo periodic breathing of at least 10 minutes duration.

The adverse consequences of SA on patients with HF are likely multifactorial. Hypoxemia and increased catecholamine output from fragmented sleep may directly lead to myocyte injury. Intrathoracic

pressure swings that occur during obstructive apneas and hypopneas (10) and during the hyperpneic phase of CSA (11) may increase transmural pressure on the right and left ventricles resulting in adverse cardiac remodeling over time. Additionally, hypertension and arterial stiffness occurring secondary to obstructive breathing disturbances may also contribute to myocardial remodeling (12). Although there is some evidence that elevations in the obstructive apnea–hypopnea index (OAH) may be an antecedent risk factor for HF (13), and although CSA/CSB has been studied in patients with established HF, the significance of an elevated central apnea index (CAI) and/or CSB is largely unknown in a relatively healthy community-based cohort.

We examined the association between SA and incident HF (either caused by new onset of ventricular dysfunction or decompensation of preexisting subclinical ventricular dysfunction) using data from the MrOS (Osteoporotic Fractures in Men) Study, a large community-based cohort of older men. Although prior data from the SHHS (Sleep Heart Health Study) (13) has examined the association between OSA and incident HF, to the best of our knowledge this is the first study to examine this association in relationships to indices of OSA and CSA and to test whether increased risk of HF or decompensation of preexisting HF caused by SA is independent of mediators, such as poor sleep quality or atrial fibrillation (AF). Some of the results of these studies have been previously reported in the form of an abstract (14).

Methods

Study Population

The sample was derived from the MrOS Study, a prospective multicenter observational study of community-dwelling older men. The initial study design, recruitment, and sample characteristics have been published elsewhere (15, 16). Data from 2,865 participants in the MrOS Sleep Study, an ancillary study of MrOS, are included in this analysis (see Figure 1 and the online supplement for more detailed methodology).

Study Protocol

During the baseline sleep visit, participants completed a series of questionnaires obtaining information about sleep,

demographics, medical history, medication use, alcohol and tobacco use, and underwent height, weight, and resting blood pressure measurements. Subsequently, participants underwent an unattended, in-home, overnight polysomnography (PSG; Sapiro, Compumedics, Inc., Melbourne, Australia) and wore a wrist actigraph (Ambulatory Monitoring, Inc., Ardsley, NY) for a minimum 5 nights and 6 days continuously except when bathing. Actigraphically measured sleep parameters included total sleep time (total hours slept while in bed) and time awake after sleep onset (WASO, total minutes of time awake from sleep onset until the end of the last sleep episode while in bed).

PSG Exposures

Primary exposures for this analysis included the CAI (calculated as total central apneas per hour sleep), the OAH (calculated as total obstructive apneas and hypopneas associated with a 3% or greater desaturation per hour of sleep), and CSB. CSB was characterized by a minimum consecutive 10-minute period of crescendo–decrescendo respiratory pattern culminating in a nadir of central apneas (17). Nocturnal hypoxemia, the percent time SaO_2 was below 90% during overnight sleep, was also measured by PSG. PSG data collection and quality codes were consistent with previously published approaches (18).

Incident HF Events

Participants were followed for potential incident cardiovascular events by postcard every 4 months for an average of 7.3 ± 2.2 years. This information and the relevant hospital records, including examination of death certificates for indication of a potential cardiovascular cause, was reviewed by a centrally trained physician to ascertain incident HF events using a formal adjudication process before inclusion in analysis. Incident HF was defined as hospital admission to treat increased intravascular volume (e.g., pulmonary edema), low cardiac output, or both.

Statistical Analysis

The sleep-disordered breathing (SDB) parameters were expressed as dichotomous variables (CAI ≥ 5 , any CSB, and OAH ≥ 15) or as quartiles (OAH). Characteristics of participants were compared across presence of SDB and incident HF status using chi-square tests for

categorical variables, Student's *t* tests for normally distributed continuous variables, and Wilcoxon rank sum tests for continuous variables with skewed distributions.

Cox proportional hazards regression was used to assess the association between SA and subsequent risk of an incident HF event, and results are presented as hazard ratios (HR) with 95% confidence intervals (CI). If an individual had more than one event, only the first event was included in analysis. Models were minimally adjusted for age, race, and clinic and then further adjusted to include body mass index (BMI), prevalent hypertension, coronary artery disease (CAD), history of diabetes,

baseline HF, stroke, physical activity, smoking status, and alcohol use. Models were further extended to include adjustment for sleep fragmentation (WASO), nocturnal hypoxemia, and prevalent AF.

Sensitivity analyses were performed excluding those with a self-report of prevalent HF and truncating the follow-up time to the start of continuous positive airway pressure (CPAP) therapy. Models with the predictors of CSB or CSA were further adjusted by OAHl to examine if the association of these predictors to incident HF was attenuated. It is possible that SDB is related to unmeasured confounders that make mortality more likely (19, 20). To

address this possibility, the Fine and Gray model was integrated to account for the competing risk of mortality (21).

All significance levels reported were two sided, and all analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Overall sample characteristics are shown in Table 1. Mean age was about 76 years. Most of the sample was white (91%) and modestly overweight (mean BMI, 27.2 ± 3.8). Approximately one-third (30%) of the sample had a prior history of CAD, a tenth

Table 1. Participant Characteristics by Incident Heart Failure

	Overall (n = 2,865)	Heart Failure (n = 174)	No Heart Failure (n = 2,691)	P Value*
Demographics				
Age, yr	76.3 $\pm$ 5.5	78.3 $\pm$ 5.5	76.2 $\pm$ 5.5	<0.0001
Race, n (%)				0.49
White	2,598 (90.7)	162 (93.1)	2,436 (90.5)	
Black	97 (3.4)	6 (3.5)	91 (3.4)	
Asian	83 (2.9)	2 (1.2)	81 (3.0)	
Hispanic	87 (3.0)	4 (2.3)	83 (3.1)	
BMI, kg/m ²	27.2 $\pm$ 3.8	27.8 $\pm$ 3.9	27.1 $\pm$ 3.8	0.01
Cardiovascular risk factors, n (%)				
Coronary artery disease†	852 (29.8)	96 (55.2)	756 (28.2)	<0.0001
Diabetes	380 (13.3)	38 (21.8)	342 (12.7)	0.0006
Hypertension	1,799 (62.8)	152 (87.4)	1,647 (61.2)	<0.0001
Stroke history	108 (3.8)	17 (9.8)	91 (3.4)	<0.0001
Heart failure	168 (5.9)	40 (23.0)	128 (4.8)	<0.0001
Atrial fibrillation	290 (11.2)	42 (27.5)	248 (10.1)	<0.0001
Tobacco use				0.06
Never	1,136 (39.7)	62 (35.6)	1,074 (39.9)	
Past	1,671 (58.3)	112 (64.4)	1,559 (58.0)	
Current	57 (2.0)	0	57 (2.1)	
Alcohol use				0.33
0–2	1,699 (59.6)	106 (61.3)	1,593 (59.5)	
3–13	998 (35.0)	62 (35.8)	936 (35)	
≥ 14	153 (5.4)	5 (2.9)	148 (5.5)	
PASE score (physical activity)	146.1 $\pm$ 71.5	133.9 $\pm$ 70.8	146.9 $\pm$ 71.5	0.02
Sleep characteristics				
Total sleep time, min	385.3 $\pm$ 73.6	380.5 $\pm$ 76.5	385.6 $\pm$ 73.4	0.38
Sleep efficiency, %	78.3 $\pm$ 11.9	74.8 $\pm$ 13.7	78.5 $\pm$ 11.7	0.0006
WASO, min‡	78.0 $\pm$ 44.2	92.8 $\pm$ 49.5	77.0 $\pm$ 43.7	<0.0001
OAHl ≥ 15 , n (%)§	1,251 (43.7)	102 (58.6)	1,149 (42.7)	<0.0001
OAHl, median (IQR)§	12.6 (6.0–23.2)	17.7 (9.3–30.3)	12.3 (6.0–22.5)	<0.0001
Central apnea index, median (IQR)	0.2 (0–0.9)	0.3 (0–1.9)	0.2 (0–0.9)	0.006
Central apnea index ≥ 5 , n (%)	209 (7.3)	24 (13.8)	185 (6.9)	0.0007
Cheyne Stokes breathing, n (%)	185 (6.5)	28 (16.1)	157 (5.8)	<0.0001
Nocturnal hypoxemia, median (IQR)	1.0 (0–3.4)	1.4 (0–4.6)	1.0 (0–3.0)	0.002

Definition of abbreviations: BMI = body mass index; IQR = interquartile range; OAHl = obstructive apnea hypopnea index; PASE = Physical Activity Scale for the Elderly; WASO = wake after sleep onset.

Data presented as mean $\pm$ SD unless otherwise specified.

*P values obtained from Student's *t* test for normally distributed continuous variables, for skewed variables a Wilcoxon rank sum test, and a chi-square test for categorical variables.

†History of coronary artery disease includes myocardial infarction, angina, bypass surgery, and angioplasty.

‡Wake after sleep onset.

§Obstructive apnea–hypopnea index.

||Percent of sleep time with oxygen saturation <90%.

Table 2. Hazard Ratio (95% Confidence Interval) of Incident Heart Failure by CSA or CSB

	Minimally Adjusted*	MV Adjusted†	MV + WASO Adjusted†	MV + OSA Adjusted†	MV + AF Adjusted†	MV + Hypoxemia Adjusted†	MV Excluding Those with Baseline HF†	MV Truncating Follow-up to Start of CPAP Use
CAI ≥5 (n = 209)	1.85 (1.20–2.86)	1.79 (1.16–2.77)	1.72 (1.11–2.67)	1.55 (0.99–2.44)	1.85 (1.17–2.94)	1.75 (1.13–2.73)	1.57 (0.92–2.66)	1.57 (0.94–2.61)
CSB (n = 185)	2.29 (1.51–3.46)	2.23 (1.45–3.43)	2.19 (1.42–3.38)	1.96 (1.26–3.07)	1.91 (1.17–3.13)	2.17 (1.41–3.35)	1.90 (1.10–3.30)	2.53 (1.60–4.00)

Definition of abbreviations: AF = atrial fibrillation; CAI = central apnea index; CPAP = continuous positive airway pressure; CSA = central sleep apnea; CSB = Cheyne-Stokes breathing; HF = heart failure; MV = multivariable; OSA = obstructive sleep apnea; WASO = wake after sleep onset.

*Adjusted for clinic site, age, race, and history of heart failure.

†Adjusted for clinic site, age, race, BMI, history of coronary artery disease (myocardial infarction, angina, bypass surgery, angioplasty), heart failure, stroke, diabetes, hypertension, smoking, alcohol use, and physical activity.

(13%) had diabetes, almost two-thirds (63%) had hypertension, and 6% already had a history of HF. The sample had a median OAH of 12.6, with almost half (46%) with an OAH greater than or equal to 15. Seven percent of the sample had a CAI greater than or equal to five, 6.5% had CSB, and 11% either had a CAI greater than or equal to five or CSB. Of the 209 individuals with CAI greater than or equal to five, 35% also had CSB, such that 2.6% of the total sample had both CSA and CSB. Furthermore, the prevalence of CSA/CSB was 6.2% in those without history of HF and 10.6% in those with a history of HF before to follow-up.

Sample characteristics by incident HF events are also shown in Table 1. Overall, 174 HF events were observed and average follow-up time was 7.3 ± 2.2 years. Compared with those without, subjects

with incident HF were approximately 2 years older; less physically active; and had a significantly higher prevalence of CAD, diabetes, hypertension, stroke, and AF. Those with incident HF events also had significantly poorer sleep quality with higher WASO, and higher levels of OAH, CAI, and nocturnal hypoxemia, and a higher prevalence of CSB.

Sample characteristics stratified by levels of CAI and OAH are presented in Tables E1 and E2 in the online supplement, respectively. Compared with those with CAI less than 5, those with a CAI greater than or equal to five (209 participants) were about 2 years older ($P < 0.0001$), less likely to smoke ($P = 0.04$), less physically active ($P = 0.01$), and more likely to have a history of AF ($P = 0.0003$) or HF ($P = 0.02$). There were no significant differences in race, BMI, or history of other cardiovascular disease

(CVD). Sample characteristics were also stratified by CSB (results not shown) and results were comparable with the CAI analysis with the exception that those with CSB were also significantly more likely to have hypertension in addition to AF and HF.

Compared with those with OAH less than 15, those with OAH greater than or equal to 15 (1,251 participants) had a higher BMI and a significantly higher prevalence of diabetes, hypertension, and HF but similar prevalence of other CVD. Only 13.4% of individuals with an OAH greater than or equal to 15 also had a CAI greater than or equal to five. There were no significant differences in race, tobacco or alcohol use, or physical activity in those with an elevated OAH compared with other participants. Participants with an elevated CAI or an elevated OAH each had significantly higher

Table 3. Hazard Ratio (95% Confidence Interval) of Incident Heart Failure by OSA Quartiles

	Minimally Adjusted*	MV Adjusted†	MV + WASO Adjusted†	MV + AF Adjusted†	MV + Hypoxemia Adjusted†	MV + Dropping Those with Baseline HF†	MV + Truncating Follow-up to Start of CPAP Use†
Quartile 1 (OAH <6)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2 (OAH 6 to <12.5)	0.87 (0.53–1.44)	0.74 (0.44–1.23)	0.74 (0.44–1.25)	0.86 (0.51–1.46)	0.73 (0.43–1.22)	0.89 (0.52–1.53)	0.76 (0.45–1.29)
Quartile 3 (OAH 12.5 to <23)	1.42 (0.90–2.25)	1.34 (0.84–2.13)	1.35 (0.84–2.15)	1.35 (0.82–2.22)	1.30 (0.80–2.14)	1.40 (0.85–2.31)	1.21 (0.74–1.97)
Quartile 4 (OAH ≥23)	1.74 (1.12–2.70)	1.42 (0.90–2.24)	1.40 (0.88–2.23)	1.45 (0.88–2.38)	1.40 (0.83–2.36)	1.29 (0.78–2.15)	1.30 (0.79–2.12)

Definition of abbreviations: AF = atrial fibrillation; CPAP = continuous positive airway pressure; HF = heart failure; MV = multivariable; OAH = obstructive apnea hypopnea index; OSA = obstructive sleep apnea; WASO = wake after sleep onset.

*Adjusted for clinic site, age, race, and history of heart failure.

†Adjusted for clinic site, age, race, BMI, history of coronary artery disease (myocardial infarction, angina, bypass surgery, and angioplasty), heart failure, stroke, diabetes, hypertension, smoking, alcohol use, and physical activity.

WASO and more nocturnal hypoxemia compared with those without. Only those with an elevated OAHl had shorter sleep duration, however. Additionally, in unadjusted analysis both groups were more likely to have incident HF events.

Table 2 demonstrates the associations of groups classified by the CAI and OAHl with incident HF events. In models adjusted for clinic site, age, race, and history of HF there was a significantly increased risk of new-onset clinical HF or HF decompensation for those with CAI greater than or equal to five (HR, 1.85; 95% CI, 1.20–2.86) compared with those with CAI less than five and for those with CSB (HR, 2.29; 95% CI, 1.51–3.46) compared with those without. This increased risk persisted after further adjustments for BMI, history of CAD, stroke, diabetes, hypertension, smoking, alcohol use, and physical activity for both CAI greater than or equal to five (HR, 1.79; 95% CI, 1.16–2.77) and CSB (HR, 2.23; 95% CI, 1.45–3.43). After further adjustment for WASO, OAHl greater than or equal to 15, hypoxemia, and AF in additional models, results were largely unchanged. In sensitivity analyses, fully adjusted models were reanalyzed after excluding participants with a history of baseline HF and after truncating follow-up time to the start of CPAP among those who initiated therapy during the follow-up period ($n = 325$). After excluding those with baseline HF, the incident risk of HF was slightly attenuated for those with CAI greater than or equal to five (HR, 1.57; 95% CI, 0.92–2.66) but remained significantly elevated for those with CSB (HR, 1.90; 95% CI, 1.10–3.30). After truncating follow-up to the start of CPAP use, the association of CAI greater than or equal to five was again attenuated (HR, 1.57; 95% CI, 0.94–2.61), whereas those with CSB had a significantly increased risk of incident HF (HR, 2.54; 95% CI, 1.60–4.00). Of the 185 participants with CSB, approximately 40% had CAI greater than or equal to five. However, additional analysis modelling by CAI and CSB separately versus a combination of CAI-CSB did not appreciably change the results.

Table 3 demonstrates the association of incident HF with quartiles of the OAHl. In minimally adjusted models, when compared with those with OAHl in the first quartile, only those with more severe OSA (fourth quartile of OAHl; OAHl ≥ 23.17)

Figure 1. Flow diagram presenting information regarding progress through the phases of the trial from MrOS Study to MrOS Sleep ancillary study to present cohort. MrOS = Osteoporotic Fractures in Men.

had a significantly increased risk of incident HF (HR, 1.95; 95% CI, 1.26–3.01). After further adjustment, however, there was no significantly increased risk of incident HF in those with an elevated OAHl.

Additional Analyses

In addition to the other covariates, models were repeated accounting for the competing risk of mortality. The multivariable fully adjusted associations of CAI and CSB with incident HF both remained significant after accounting for the competing risk of mortality (HR, 1.69; 95% CI, 1.08–2.65 for CAI ≥ 5) (HR, 2.17; 95% CI, 1.38–3.41 for CSB). Analyses were also repeated using nocturnal hypoxemia because the exposure and results were similar to that of OSA quartiles. When compared with those with no nocturnal hypoxemia (% sleep time with $\text{SaO}_2 < 90\%$), those with greater than or equal to 10% of sleep time with SaO_2 less than 90% had an increased risk of incident

HF only in the minimally adjusted models (HR, 1.72; 95% CI, 1.10–2.71) but not after adjusting for other covariates.

Discussion

Our results demonstrate that in a community-based cohort of older men, after adjusting for confounders and potential mediators, presence of an elevated CAI or CSB predicts increased risk of incident HF events, defined as HF decompensation or new-onset ventricular dysfunction. To the best of our knowledge this is the first study demonstrating increased risk of incident HF with CSA as defined as an elevated CAI and/or CSB. However, given the prior literature demonstrating a strong cross-sectional association between CSA and HF and evidence that effective treatment of CSA improves outcomes (6, 7, 22), these findings are fitting.

Additionally, our results demonstrate that CSB, measured simply as a dichotomous exposure identified on the PSG record, is a stronger predictor of incident HF events than is an elevation of the CAI, particularly after excluding participants with a prior history of HF and truncating follow-up time to the start of CPAP in sensitivity analysis. This may be because the presence of CSB may more reliably identify specific abnormalities in ventilation than CAI, such as elevations in circulation time, which may identify those who are further along the spectrum of subclinical cardiac dysfunction and more likely to convert to clinically overt HF. Alternatively, it is possible that measurement of central apneas using standard respiratory sensors and without consideration of central hypopneas may have led to more misclassification than a simple approach of identifying CSB through pattern recognition of crescendo-decrescendo breathing. Additionally, because risk increased after truncating time to start of therapy in those who initiated CPAP during the follow-up period, this suggests that use of PAP may mitigate this risk.

There are several mechanisms that may explain the observed associations. The intrathoracic pressure swings during the hyperpneic phase of CSB (11) following a central apnea increase the transmural pressure of the left and right ventricles, which may over time lead to increased ventricular afterload resulting in adverse cardiac remodeling. Additionally, prior work demonstrates increased nocturnal urinary and plasma norepinephrine on awakening in those with CSA and HF compared with those without CSA (23). The increased sympathetic nervous system activity may result in increased cardiac stress by elevating nocturnal blood pressure and heart rate.

OSA, identified as either an elevated OAHl or by quartiles of OAHl, however, was not a significant predictor of incident HF after adjusting for prevalent CVD and other confounders. Prior data from the SHHS demonstrated that middle-aged and older men with an elevated AHI (calculated by considering both central and obstructive events) were at increased risk of incident HF (HR, 1.13; 95% CI, 1.02–1.26). In SHHS, men with an AHI greater than or equal to 30 were 58% more

likely to develop HF than those with AHI less than five (13). Because of differences in how SDB were defined in these analyses, it is not possible to directly compare the results with the current study. However, the effect size in the current study for the top OAHl quartile (OAHl ≥ 23.17 ; HR, 1.42) was similar to the SHHS HR top AHI category of 1.58; the wider CI may have reflected differences in sample size (SHHS included 4,422 participants). It is possible that there is a stronger association between obstructive events and HF in middle-aged compared with older individuals. In particular, subjects in SHHS were significantly younger (median age, 62) (13) compared with those in MrOS (mean age, 76). Supportive of this are data demonstrating that the increased risk of cardiovascular events and mortality (24) in subjects with OSA are primarily in those aged 30–50 (25). The current analysis also highlights the potential importance in distinguishing between CSA and OSA in analysis of incident CVD.

There are several strengths to this study. Use of a community-based cohort minimized referral biases and use of standardized and objective measures of OSA and CSA-CSB with PSG and of sleep quality with actigraphy minimized measurement error and reporting biases and extends prior literature. Other strengths included the use of a central physician adjudicator following an explicit protocol to identify incident HF events and the detailed prospective collection of information on covariates, such as other CVD events, accounting for the competing risk of mortality, and the inclusion of actigraph measured poor sleep quality data as a potential mediator.

There are also several limitations worthy of note. First, this study was limited to older men and therefore results are less generalizable to the population at large. In particular, given that younger individuals with OSA may be at higher cardiovascular risk than older subjects, and that the older age of our participants may bias results with a healthy survivor effect, our study may underestimate the risk of incident HF in those with OSA. The definition of CSB was based on consensus agreement by the American Academy of Sleep Medicine (17) and prior literature (26), which is commonly used in clinical settings, to allow for the greatest

interpretability. However, a more quantitative method for defining CSB may have been more informative. More precise quantification of central events, including identification of central hypopneas, may have improved the predictive value of central events.

Furthermore, although formal adjudication of incident HF was centrally performed according to a well-defined protocol, results were not confirmed with echocardiography. Additionally, we did not distinguish between HF with preserved versus reduced ejection fraction or ascertain New York Heart Association class in participants. Finally, although in sensitivity analyses we excluded individuals with baseline self-reported CHF, it is possible that subclinical cardiac dysfunction was present among the individuals with CSA-CSB and therefore we cannot conclude that CSA-CSB truly predicts incident HF because it is possible that it modulates the natural history of ventricular dysfunction making those with subclinical HF more likely to decompensate into clinically overt HF.

In summary, this study demonstrates that individuals with an elevated CAI and/or CSB, but not an elevated OAHl, are at increased risk for incident HF events. These associations persist after adjusting for confounders. Our results extend prior literature by considering the influence of central and obstructive events, and by incorporating objective measures of sleep quality as covariates. These results suggest that screening individuals with CSA and/or CSB for occult HF may be important and that providing effective treatment of their SDB may mitigate this risk. Although typically CSB is considered to be a consequence of HF, our results suggest that CSA and/or CSB may precede the onset of clinically overt HF. Further research is needed to understand whether central events provide markers of subclinical cardiac disease or whether their occurrence represents pathophysiologic breathing that increases risk of incident HF independently of cardiac dysfunction. ■

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