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Prevalence and Predictors of Sleep-Disordered Breathing in Patients With Stable Chronic Heart Failure

The SchlaHF Registry

Michael Arzt, MD,[a] Holger Woehrle, MD,[b,c] Olaf Oldenburg, MD,[d] Andrea Graml, Dipl Stat,[c] Anna Suling, PhD,[e] Erland Erdmann, MD,[f] Helmut Teschler, MD,[g] Karl Wegscheider, PhD,[e] for the SchlaHF Investigators

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CME Objective for This Article: After reading this article, the reader should be able to discuss: 1) how sleep-disordered breathing can be assessed in patients with heart failure; 2) the prevalence of sleep-disordered breathing in patients with chronic heart failure with reduced ejection fraction; and 3) risk factors associated with sleep-disordered breathing in patients with chronic heart failure with reduced ejection fraction.

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From the [a]Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany; [b]Sleep and Ventilation Center Blaubeuren, Respiratory Center Ulm, Ulm, Germany; [c]ResMed Science Center, Martinsried, Germany; [d]Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Bad Oeynhausen, Germany; [e]Department of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [f]Clinic III for Internal Medicine, Heart Center University Hospital Cologne, Cologne, Germany; and the [g]Department of Pneumology, Ruhrlandklinik, West German Lung Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany. The SchlaHF registry was funded by ResMed Ltd. (Sydney, Australia) and ResMed Germany Inc. (Martinsried, Germany). ResMed also provided funding for English language editing

Prevalence and Predictors of Sleep-Disordered Breathing in Patients With Stable Chronic Heart Failure

The SchlaHF Registry

ABSTRACT

OBJECTIVES This prospective study investigated the prevalence of sleep-disordered breathing (SDB) and its predictors in patients with stable chronic heart failure (HF).

BACKGROUND SDB is increasingly recognized as being important in patients with HF.

METHODS The multicenter SchlaHF (Sleep-Disordered Breathing in Heart Failure) registry provides demographic and clinical data on chronic, stable, symptomatic patients with HF (New York Heart Association functional class ≥II; left ventricular rejection fraction ≤45%). Moderate-to-severe SDB (apnea-hypopnea index ≥15/h) was determined by a 2-channel screening device (ApneaLink, ResMed, Sydney, Australia).

RESULTS Data from 6,876 patients were analyzed. The prevalence of moderate-to-severe SDB was 46%, with a significant sex difference: 36% in women (n = 1,448) versus 49% in men (n = 5,428). Prevalence of SDB rose with increasing age (31%, 39%, 45%, 52%, and 59% in those age ≤50, >50 to 60, >60 to 70, >70 to 80, and >80 years, respectively). Risk factors for SDB were body mass index (per 5 units; odds ratio [OR]: 1.29; 95% confidence interval [CI]: 1.22 to 1.36), left ventricular rejection fraction (per 5% decrement from 45%; OR: 1.10; 95% CI: 1.06 to 1.14), age (per 10-year difference to 60 years; OR: 1.41; 95% CI: 1.34 to 1.49), atrial fibrillation (OR: 1.19; 95% CI: 1.06 to 1.34), and male sex (OR: 1.90; 95% CI: 1.67 to 2.17).

CONCLUSIONS SchlaHF registry data demonstrate a high prevalence of SDB in a representative population of stable patients with chronic HF receiving contemporary medical management. Male sex, age, body mass index, and the severity of both symptoms and left ventricular dysfunction were clinical predictors for prevalent SDB. (Prevalence, Clinical Characteristics and Type of Sleep-disordered Breathing in Patients With Chronic, Symptomatic, Systolic Heart Failure; NCT01500759) (J Am Coll Cardiol HF 2016;4:116–25) © 2016 by the American College of Cardiology Foundation.

Chronic heart failure (HF) is a symptomatic, debilitating disease. Patients require frequent hospitalization, and the mortality rate is high (1,2). Guideline-driven pharmacological treatment and cardiac resynchronization therapy (3,4) have improved outcomes for many patients. However, a significant number of those with chronic HF still experience persistent symptoms, and most of them will die from cardiovascular causes, usually progressive HF (1,2). A complementary strategy

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ABBREVIATIONS AND ACRONYMS

AHI = apnea-hypopnea index

BMI = body mass index

CI = confidence interval

CSA = central sleep apnea

CSR = Cheyne-Stokes respiration

HF = heart failure

LVEF = left ventricular rejection fraction

NYHA = New York Heart Association

OR = odds ratio

OSA = obstructive sleep apnea

PSG = polysomnography

SDB = sleep-disordered breathing

for the management of HF might be to identify alternative and additional features that contribute to disease progression and impair prognosis, and then develop strategies to target, improve, and overcome these factors (5).

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Sleep-disordered breathing (SDB) is 1 condition that is under investigation as a contributor to symptom burden (6), morbidity, and mortality in patients with chronic HF (5,7–9). The prevalence of comorbid SDB in patients with HF is high, at 47% to 76% (10–14). SDB is characterized by 2 different abnormal breathing patterns: obstructive sleep apnea (OSA) and central sleep apnea (CSA) with Cheyne-Stokes respiration (CSR). The prevalence of OSA was reported to be higher in patients with chronic HF (12% to 43%) than in the general population (15–20). The prevalence of CSA-CSR in patients with chronic HF ranges between 21% and 40% in different studies (10–14). Furthermore, both OSA and CSA-CSR have been shown to be markers of disease severity and predictors of increased mortality in chronic HF (8,21–25).

In general, the reported prevalence of SDB in chronic HF is based on either single-center or small-scale studies. To date only 1 multicenter study has been reported (12), and just 5 single-center studies enrolling ≥100 participants have been published (10–14). Furthermore, in all previous studies, women were a minority of participants, which does not allow robust sex-specific estimates of SDB prevalence (10–14). All samples included highly selected patients with chronic HF who were either hospitalized patients or outpatients from specialist HF clinics (10–14,26). This resulted in populations that were predominantly male and younger than the average patient with chronic HF (2,26–28).

The clinical diagnosis of SDB in patients with chronic HF is difficult because key symptoms and characteristics of patients with SDB and normal cardiac function, such as daytime sleepiness and obesity, are often not present (29,30). This means that the rate of sleep testing in patients with chronic HF is very low (31). Clinical predictors for SDB have not been studied in a large sample of stable patients with chronic HF who were not pre-selected according to potential SDB-related symptoms.

This study analyzed a large representative sample of patients with chronic HF from cardiology practices and hospital departments. The aim was to prospectively determine the prevalence of SDB and clinical predictors for the disease that are routinely assessed in the clinical work-up of patients with chronic HF.

METHODS

DESIGN OVERVIEW. In the German SchlaHF (Sleep-Disordered Breathing in Heart Failure) registry, assessment of SDB was performed in 256 centers using a 2-channel respiratory monitor (ApneaLink, ResMed, Sydney, Australia). The rationale and design of the SchlaHF registry have been described in detail elsewhere (32). All German sleep laboratories were invited to participate in the registry. However, most did not have the infrastructure necessary to run such a project and therefore built networks with cardiologists in their referral area. Participating cardiologists, who had been contacted by and were working with sleep laboratories, were asked to consecutively enroll all patients with HF who fulfilled the registry inclusion criteria described later.

Age, body mass index (BMI), sex, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, heart rhythm, nocturnal dyspnea symptoms, nocturia, apnea-hypopnea index (AHI), HF etiology, and medication were documented for 6,876 stable patients with chronic HF between February 2008 and January 2011 at 138 centers in Germany (91 cardiology practices and 47 hospital departments). Oxygen desaturation index, average oxygen saturation (mean Sp_{O_2}), and minimum oxygen saturation (min Sp_{O_2}) were documented in 97% of patients, respectively. The SchlaHF registry received central ethics approval from the Freiburger Ethikkommission for Germany. All aspects of the registry were conducted within the principles of Good Clinical Practice and in accordance with the Declaration of Helsinki. All participants provided written informed consent.

PARTICIPANTS. The inclusion criteria were as follows: chronic HF diagnosed and treated according to the European Society of Cardiology guidelines (4) ≥12 weeks before enrollment; moderate-to-severe left ventricular systolic dysfunction (LVEF ≤45% by an imaging method, such as echocardiography, radionuclide angiography, left ventriculography, or cardiac magnetic resonance imaging) documented <12 weeks before enrollment; NYHA functional class III or IV at the time of inclusion, or NYHA functional class II with ≥1 hospitalization for HF in the last 12 months; and patient able to fully understand the information about the SchlaHF registry and give written informed consent. Patients were excluded if they had

any of the following: current use of positive airway pressure therapy; life expectancy <1 year for diseases unrelated to chronic HF-with reduced ejection fraction (REF); cardiac surgery, percutaneous coronary intervention, myocardial infarction, or unstable angina within 6 months before randomization; cardiac resynchronization therapy implantation scheduled or performed within 6 months before randomization; transient ischemic attack or stroke within 3 months before enrollment; primary hemodynamically significant uncorrected valvular heart disease (obstructive or regurgitant) or any valvular disease expected to require surgery; and acute myocarditis/pericarditis within 6 months before enrollment.

ASSESSMENT OF SDB. Nasal flow and pulse oximetry were measured using the ApneaLink device (ResMed) that has been validated in several studies for screening of SDB (33-38). Comparing ApneaLink (using automatic scoring) with the gold standard polysomnography (PSG) in patients without known heart disease, studies have reported a sensitivity of 73% to 94% and a specificity of 85% to 95% using an AHI cutoff value of 15/h.

In a subset of patients with chronic HF from the SchlaHF-Registry (n = 65), ApneaLink (using automatic scoring) was performed simultaneously with PSG as described in detail in the Online Appendix. For detecting SDB (AHI ≥15/h) assessed by PSG (manual scoring), the ApneaLink (automatic scoring) had a sensitivity of 73%, a specificity of 87%, a positive predictive value of 86%, and a negative predictive value of 74%.

The default settings of the screening device were used for the definitions of apnea, hypopnea, and desaturation: apnea was defined as a ≥80% decrease in airflow for ≥10 s; hypopnea was defined as a decrease in airflow by ≥50% to 80% versus baseline for ≥10 s; desaturation was defined as a ≥4% decrease in oxygen saturation; and SDB was defined as AHI ≥15/h. Of the 138 cardiology centers, 8 used respiratory polygraphy and 7 used polygraphy or ApneaLink for screening of SDB. When the ApneaLink was used, automatic scoring of respiratory events was accepted.

STATISTICAL ANALYSIS. Descriptive statistics were absolute and relative frequency or mean ± SD, whatever appropriate. Because prevalences varied considerably between centers (cardiology practices or departments) presumably reflecting differences in patient populations, all inferential statistics were calculated with centers as a random term. Random effects logistic regression was used to model the association between suspected causes of SDB and the risk of developing that disorder. Linear mixed models were applied for the severity analysis of SDB in patients with an AHI ≥15/h. The models included the same set of potential clinical predictors of SDB: age, BMI, sex, LVEF, NYHA functional class, atrial fibrillation, and ischemic origin. For the study of sex differences, interaction terms with sex were added to the model if selected by backward elimination based on likelihood ratio tests. Results are visualized by forest plots showing adjusted odds ratios (ORs) and by marginal means (here, adjusted SDB prevalence). Although age, BMI, LVEF, and EF were modelled as continuous linear predictors for

TABLE 1 Demographic and Clinical Characteristics

	Patients With Chronic HF		Total Patients (n)
	No SDB	SDB	
n	3,686 (54)	3,190 (46)	6,876
Age, yrs	65 ± 12	69 ± 11*	6,876
BMI, kg/m^2	28.1 ± 5.0	28.9 ± 5.2*	6,876
Male	2,754 (75)	2,674 (84)*	6,876
LVEF, %	33.6 ± 8.0	32.8 ± 8.3*	6,876
NYHA functional class ≥III	2,566 (70)	2,341 (73)*	6,876
Ischemic etiology	1,961 (53)	1,742 (55)	6,876
Atrial fibrillation	863 (23)	1,001 (31)*	6,876
Nocturnal dyspnea	672 (19)	800 (25)*	6,766
Nocturia ≥3 times/night	580 (16)	660 (21)*	6,776
AHI, /h	6 ± 4	31 ± 14*	6,876
ODI, /h	8 ± 10	24 ± 15*	6,711
Mean Spo_2, %	93 ± 2	92 ± 3*	6,693
Min Spo_2, %	83 ± 6	80 ± 6*	6,667
Medication			
ACE inhibitors and/or ARBs	3,269 (89)	2,812 (88)	6,876
Beta-blockers	3,284 (89)	2,824 (89)	6,876
Diuretics	2,805 (76)	2,617 (82)*	6,876
Digitalis	717 (19)	599 (19)	6,876
Aldosterone antagonists	1,808 (49)	1,454 (46)*	6,876

Values are n (%) or mean ± SD. SDB was defined as AHI ≥15/h. No SDB was defined as AHI <15/h.
*p < 0.05 versus patients with no SDB.

ACE = angiotensin-converting enzyme; AHI = apnea/hypopnea index; ARBs = angiotensin receptor blockers; BMI = body mass index; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ODI = oxygen desaturation index; SDB = sleep-disordered breathing; Spo_2 = oxygen saturation.

TABLE 2 Observed Prevalence of SDB by Age and Sex

	SDB Prevalence (% Patients)	
Age, yrs	Males	Females
18–50	35	16*
50–60	42	25*
60–70	47	35*
70–80	55	41*
>80	62	47*

Values are marginal mean. SDB was defined as apnea-hypopnea index ≥15/h.
*p < 0.05 versus males.

SDB = sleep-disordered breathing.

TABLE 3 AHI in all Patients With SDB, and by Sex and Age

	AHI (/h)		
	All Patients	Male	Female
Overall	31 ± 14	32 ± 14	29 ± 14*
Age, yrs			
18-50	32 ± 16	32 ± 16	25 ± 10*
50-60	31 ± 15	32 ± 15	27 ± 13*
60-70	30 ± 13	31 ± 13	27 ± 12*
70-80	31 ± 13	32 ± 13	30 ± 15
>80	33 ± 14	34 ± 14	30 ± 14

Values are mean ± SD. *p< 0.05 versus males.
Abbreviations as in Table 1.

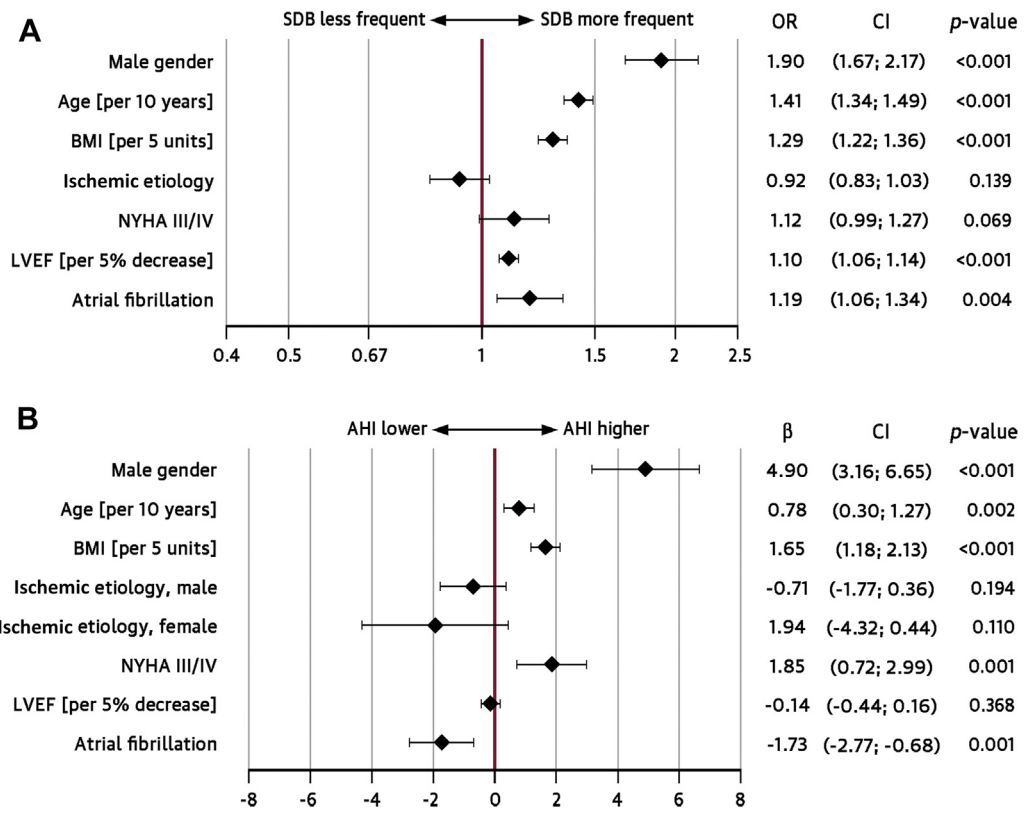
the forest plots, they were classified to allow a graphical presentation of the prevalence.

A p value <0.05 was considered to be statistically significant. Statistical analysis was performed with SPSS version 22.0 (SPSS Inc., Chicago, Illinois) and STATA version 13.0 (STATA Corporation, College Station, Texas).

RESULTS

PATIENT CHARACTERISTICS. Data from 6,876 stable patients with chronic HF were included in this analysis. Patients with SDB were older, had a higher BMI, and were more likely to be male (Table 1). Patients with chronic HF with SDB had more severe HF (higher NYHA functional class and higher prevalence of atrial fibrillation). In addition, such symptoms as nocturnal dyspnea and nocturia (≥3 times/night) occurred significantly more often in individuals with SDB. The causes of chronic HF, such as ischemia, were similar in both groups, as was use of most HF medication. However, patients with SDB were significantly more likely to be using diuretic agents and significantly less likely to be taking an aldosterone antagonist compared with those without SDB.

FIGURE 1 Predictors of Sleep-Disordered Breathing and Apnea-Hypopnea Index



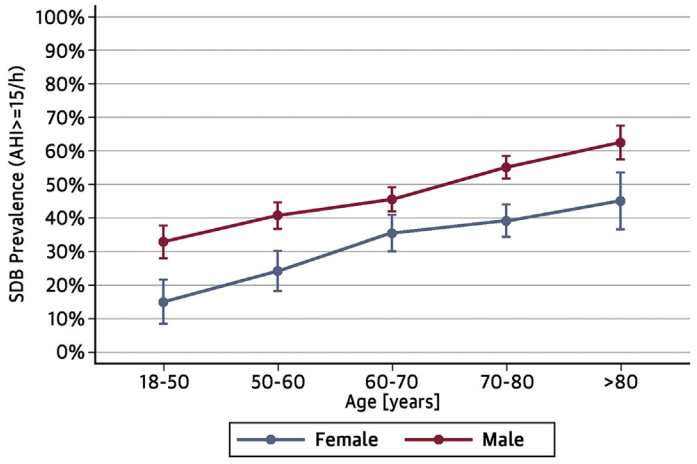
Influence of different patient characteristics on **(A)** the prevalence of SDB (AHI ≥15/h) in patients with chronic heart failure and **(B)** the severity of SDB (quantified by AHI) in patients with chronic heart failure and SDB (AHI ≥15/h). AHI = apnea-hypopnea index; BMI = body mass index; CI = confidence interval; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OR = odds ratio; SDB = sleep-disordered breathing.

PREVALENCE OF SDB IN PATIENTS WITH CHRONIC HF. The prevalence of SDB was 36% in women, 49% in men, and 46% overall. The prevalence of SDB increased with age and was numerically higher in males in any age group (Table 2). In patients with SDB, mean AHI was higher in men than in women, both overall and in the different age groups (Table 3).

CLINICAL PREDICTORS FOR SDB. Because predictors of SDB act simultaneously, it is required to analyze them in multivariate models. Random effects logistic regression showed that in chronic HF, SDB was independently associated with male sex (OR: 1.90; 95% confidence interval [CI]: 1.67 to 2.17; $p < 0.001$), age (per 10 years; OR: 1.41; 95% CI: 1.34 to 1.49; $p < 0.001$), BMI (per 5-U increment; OR: 1.29; 95% CI: 1.22 to 1.36; $p < 0.001$), LVEF (per 5% decrease; OR: 1.10; 95% CI: 1.06 to 1.14; $p < 0.001$), and atrial fibrillation (OR: 1.19; 95% CI: 1.06 to 1.34; $p = 0.004$). Conversely, ischemic etiology (OR: 0.92; 95% CI: 0.83 to 1.03; $p = 0.139$) and NYHA functional class ≥III (OR: 1.12; 95% CI: 0.99 to 1.27; $p = 0.069$) were not significant (Figure 1A). Adjusted SDB prevalence rates by age and sex are shown in Figure 2. Figure 3 shows adjusted SDB prevalence based on BMI and LVEF.

CLINICAL PREDICTORS FOR AHI IN PATIENTS WITH SDB. Multivariate analysis showed that higher AHI in patients with SDB was independently associated with male sex (regression coefficient, 4.90; 95% CI: 3.16 to 6.65; $p < 0.001$), age (per 10 years; OR: 0.78; 95% CI: 0.30 to 1.27; $p = 0.002$), BMI (per 5-unit increment; OR: 1.65; 95% CI: 1.18 to 2.13; $p < 0.001$), NYHA functional class ≥III versus class II (OR: 1.85; 95% CI: 0.72 to 2.99; $p = 0.001$), and atrial fibrillation (OR: -1.73; 95% CI: -2.77 to -0.68; $p = 0.001$). LVEF and ischemic etiology in men and women did not show a significant independent association with AHI ($p = 0.368$, $p = 0.194$, and $p = 0.110$, respectively) (Figure 1B).

FIGURE 2 SDB Prevalence by Sex and Age Group



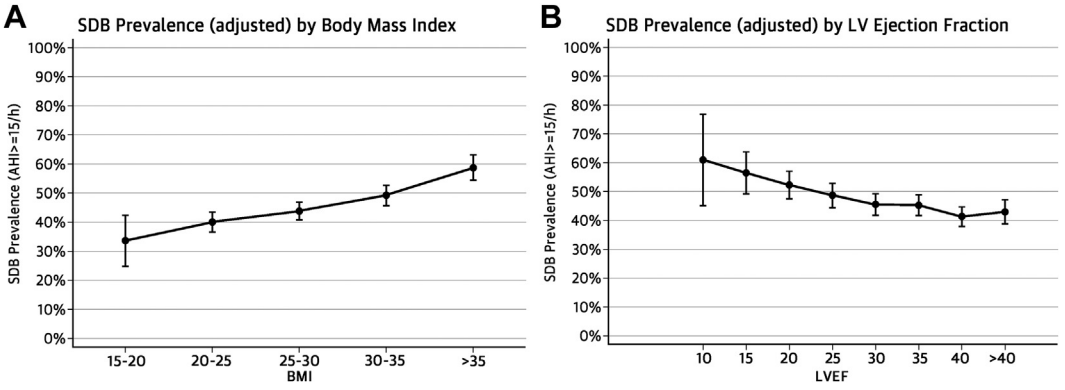
Prevalence of SDB (AHI ≥15/h) in patients with chronic heart failure by age and sex, adjusted for all other risk factors in the model. Abbreviations as in Figure 1.

DISCUSSION

This analysis of the prospective SchlaHF registry reports several robust findings. First, moderate-to-severe SDB is very common in a large representative population of patients with stable chronic HF receiving optimized medical treatment: 46% in a sample of 6,876 patients. Prevalence was dependent on both age and sex. The sex difference was constant over the total age range after accounting for other risk factors for SDB in HF. Second, male sex, older age, higher BMI (kg/m^2), more severe impairment of systolic cardiac function (i.e., lower LVEF), higher NYHA functional class, and atrial fibrillation were clinical predictors for at least moderate SDB. Third, the extent of AHI in patients with SDB is greater in males, patients who are older, with higher BMI, and with higher NYHA functional class.

The observed high prevalence of SDB in the SchlaHF registry is in accordance with most of the 5 previous studies that included more than 100 patients with chronic HF. Discrepancies can be explained in most cases by differences in patient populations and methodology applied to measure SDB. For example, Sin et al. (13) reported an SDB prevalence of 61% in 450 consecutive patients with stable chronic HF (85% male, 15% female). The higher prevalence of SDB in this study can be explained by the fact that this study was not designed to determine the prevalence of SDB in patients with HF. Instead, the HF sample was preselected by referral to the sleep laboratory because of a suspected sleep disorder, and scoring rules of PSG in this study allowed classification of respiratory events as hypopneas in the absence of an arousal or oxygen desaturation (13). In another study, the prevalence of SDB of any severity (AHI ≥5/h) in a population of 218 patients with chronic HF (23% of who were female) was 47% (14). This value is very similar to that reported in the present study because although the population was younger (age 56 years vs. 66 years), this was counterbalanced by worse left ventricular function (LVEF 25% vs. 34%). A high prevalence of SDB in HF was reported in other studies as well. The largest study to date

FIGURE 3 SDB Prevalence by Body Mass Index and Left Ventricular Ejection Fraction



Prevalence of SDB (AHI ≥15/h) in patients with chronic heart failure by BMI **(A)** and LVEF intervals **(B)**, adjusted for all other risk factors in the model. Abbreviations as in Figures 1 and 2.

prospectively enrolled 700 patients (20% female) (11). SDB was documented in 76% of patients (40% with CSA and 36% with OSA) (11). Looking at moderate-to-severe SDB (AHI ≥15/h), the prevalence was 52% (11). Patients with CSA or OSA were older than those without SDB and were more likely to be male. In addition, patients with CSA had more advanced HF symptoms and were more likely to have atrial fibrillation, and those with OSA had a higher BMI and tended to have a higher prevalence of diabetes (11). The overall prevalence of SDB in another study of 100 male patients with chronic HF was also approximately 50% (10).

Obviously, the use of different AHI thresholds to define SDB is associated with variation in prevalence rates. For instance, Schulz et al. (12) performed a multicenter study using an AHI ≥10/h as the SDB definition and found a prevalence of 71% in 203 patients with chronic HF (25% female). Age, BMI, and AHI in this study were similar to those in the current analysis, and therefore the different definition of SDB (AHI ≥10/h vs. ≥15/h) was probably a big contributor to the different prevalence rates reported, although a lower LVEF in the Javaheri (10) study population could also have played a role.

In summary, the prevalence rate observed in this large population analysis was lower than that in previous studies that included younger patients with a greater degree of left ventricular dysfunction (10–14). The older age and better cardiac function in this trial can probably be explained by the fact that patients were identified through cardiology practices, whereas those in previous studies were mostly recruited or referred from specialized HF clinics in hospitals.

In the Sleep Heart Health Study, Young et al. (20) reported the average age-dependent SDB prevalence in community-dwelling adults age 39 to 99 years.

TABLE 4 Risk Factors for SDB in Chronic Heart Failure

First Author, Year (Ref.)	Setting	Patients (n)	Source of Patients	SDB Diagnosis	Female, n (%)	ß-Blocker (%)	Spironolactone (%)	Risk Factors for SDB
Sin et al., 1999 (13)	Single center	450	Sleep laboratory referrals	PSG	68 (15)	0	0	CSA: male, age ≥60 yrs, Pco_2 ≤38 mm Hg, AF OSA: BMI (men); age (women)
Yumino et al., 2009 (14)	Single center	218	Heart failure clinic	PSG	50 (23)	75	21	CSA: male, age, AF, lower Pco_2, diuretic use OSA: male, age, BMI
MacDonald et al., 2008 (26)	Single center	108	Heart failure clinic	SDB-screening device	16 (15)	82	36	SDB: AF, NYHA functional class
Arzt et al. (SchlaHF)	Multicenter	6,876	Cardiology practices and hospital departments	SDB-screening device	1,448 (21)	89	47	SDB: Male, age, BMI, LVEF, AF (no sex differences for significant risk factors)

AF = atrial fibrillation; CSA = central sleep apnea; OSA = obstructive sleep apnea; Pco_2 = carbon dioxide pressure; PSG = polysomnography; pts = patients; SchlaHF = Sleep-Disordered Breathing in Heart Failure; other abbreviations as in Table 1.

The results showed SDB prevalence, defined as AHI ≥15/h, increased between 40 and 60 years of age from 6% to 20%, reaching a plateau between age 60 and 70 years. In contrast, we could not find such a plateau effect in our population of patients with chronic HF. Instead there was a continuous increase in SDB prevalence, from 31% in the subgroup age ≤50 years to 57% in the oldest patients (age >80 years).

Evaluation of which clinical characteristics assessed as part of the routine work-up of patients with chronic HF might help clinicians to predict those likely to have SDB would be helpful in the management of the condition, enabling risk stratification and reducing symptom burden and morbidity in selected patients. The role of treatment for OSA and/or CSA in patients with HF remains to be determined (39). In this context, the recently published results from the SERVE-HF (Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure) trial (NCT00733343) provide new and important information (40).

SERVE-HF was a multinational, multicenter, randomized controlled trial designed to assess whether treatment of moderate-to-severe predominant CSA with adaptive servoventilation, in addition to guideline-based medical therapy, reduced morbidity and mortality in patients with chronic stable HF and reduced ejection fraction (41). The primary endpoint was a composite of all-cause mortality and hospitalization for worsening HF, and there was no statistically significant difference between patients in the adaptive servoventilation group compared with those receiving guideline-based medical therapy alone (control subjects) (hazard ratio: 1.13; 95% CI: 0.97 to 1.31; p = 0.10) (40). However, additional analysis showed that patients in the adaptive servoventilation group had an increased risk of both all-cause mortality (hazard ratio: 1.28; 95% CI: 1.06 to 1.55; p = 0.01) and cardiovascular mortality (hazard ratio: 1.34; 95% CI: 1.09 to 1.65; p = 0.006) versus control subjects (40). Potential mechanisms that might explain these unexpected results remain unclear (42).

Male sex, age, obesity, severe impairment of systolic cardiac function, NYHA functional classes III and IV, and atrial fibrillation were independently associated with SDB or increased AHI in this study. Perhaps 1 of the most interesting results was that there were no sex differences in the significant predictors of SDB and AHI, despite analyses designed to detect such differences. This suggests that although the prevalence of SDB differs in men and women, the underlying disease mechanisms are the same.

So far, only 3 other studies have reported independent predictors of SDB obtained using multivariate analysis (**Table 4**) (13,14,26). Male sex, atrial fibrillation, low awake carbon dioxide pressure, age in general, and age >60 years were independently associated with CSA-CSR (13,14). In OSA, both Sin et al. (13) and Yumino et al. (14) demonstrated that BMI was a predictor only in men. However, these 2 studies reported different observations on the role of age; Sin et al. (13) found that age was an independent predictor of OSA in women only, whereas Yumino et al. (14) reported this association for both sexes. Furthermore, Yumino et al. (14) showed that atrial fibrillation was independently associated with OSA. MacDonald et al. (26) identified atrial fibrillation and NYHA functional class III and IV as risk factors for SDB, independent of sex, age ≥60 years, BMI, and LVEF. Other studies, which did not perform multivariate analyses, reported worse functional classification and LVEF <20% as markers for CSA (10,11).

This study has 3 major strengths. First, because of the large sample size, the prospective recruitment of patients by both cardiology practices and hospital cardiology departments, and the use of a portable screening device for SDB instead of PSG, the results are more representative and applicable to contemporary chronic HF population than previous studies (13,14,26). This study cohort is similar to the community chronic HF population described by Redfield et al. (28) in terms of age (63 years vs. 66 years), BMI (28.4 kg/m^2 vs. 28.4 kg/m^2), and proportion of women (26% vs. 21%). Assessment of SDB with PSG as it was done by Sin et al. (13), Yumino et al. (14), and other investigators is the gold standard for diagnosing SDB. However, performing a time-consuming in-laboratory/in-hospital sleep study confers a major selection bias itself. For example, in the "HypnoLaus study" (43), 875 of the 3,043 patients (29%) who were invited for PSG refused to undergo this diagnostic test. Therefore, the prevalence and risk factor estimates in the SchlaHF study are likely to be the most representative reported to date. Second, because this was the first large-scale study in a representative study cohort, it was possible to present age- and sex-dependent prevalence and risk factor estimates; this is in contrast to previous studies (13,14,26). Third, we could confirm predictors, such as male sex, age, obesity, and atrial fibrillation as reported by previous studies (13,14) in a larger patient population. Furthermore, this is the first study that presents an independent association between SDB and both severe impairment of systolic cardiac function and higher NYHA functional class.

STUDY LIMITATIONS. Our study does also have some limitations. We studied SDB prevalence by using the screening device ApneaLink instead of gold standard PSG. PSG was not performed in a representative sample of patients with HF and therefore it was not possible to differentiate between OSA and CSA with respect to prevalence or risk factors. The device was evaluated in several studies versus PSG (33-38). These studies reported an excellent correlation between results obtained by PSG and ApneaLink. Hence, ApneaLink seems to be an accurate screening tool for SDB in a population with high prevalence of the disorder. Although Ragette et al. (37) showed that ApneaLink might slightly overestimate AHI, the results of the validation study in a subset of patients from the SchlaHF Registry (Online Appendix) suggest that ApneaLink might underestimate AHI. This is plausible because the number of apneas and hypopneas are reported in relation to "total recording time" with ApneaLink compared with "total sleep time" with PSG. Thus, the use of ApneaLink is likely to result in conservative prevalence estimates. Because we reported prevalence for SDB overall, and not for the subgroups of OSA and CSA, we cannot exclude the possibility that the risk factors identified relate only to 1 of these conditions, rather than both.

Growing evidence suggests that SDB may play an important role in patients with HF and preserved ejection fraction (5). The SchlaHF registry only includes patients with HF and reduced ejection fraction because at the time the registry was designed, the relationship between SDB and HF with preserved ejection fraction was not well known.

CONCLUSIONS

The SchlaHF registry data demonstrate a high prevalence of SDB in a representative population of stable patients with chronic HF with contemporary medical management. Male sex, age, BMI, and the severity of both symptoms and left ventricular dysfunction were clinical predictors for the presence of SDB.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Michael Arzt, Schlafmedizinisches Zentrum, Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany. E-mail: michael.arzt@klinik.uni-regensburg.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The pretest probability of a patient with chronic HF and reduced ejection fraction being treated with optimized medical treatment having clinically relevant SDB with ≥15 apneas and hypopneas per hour is approximately 50%. Data from the SchlaHF registry, and the fact that patients with chronic HF with SDB often do not show typical SDB symptoms, suggest that the presence of 1 or more predictors of SDB, such as male sex, older age, obesity, ejection fraction <25%, or NYHA functional class III/IV, should prompt clinicians to perform device-based screening for SDB.

TRANSLATIONAL OUTLOOK: In view of the various phenotypes of SDB and their potential differential clinical implications in chronic HF, the development of easy to use screening devices for SDB with the ability to discriminate between OSA and CSA with and without periodic breathing is warranted. This could be useful for risk stratification in patients with chronic HF.

REFERENCES

1. Cubbon RM, Gale CP, Kearney LC, et al. Changing characteristics and mode of death associated with chronic heart failure caused by left ventricular systolic dysfunction: a study across therapeutic eras. Circ Heart Fail 2011;4:396–403.

2. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007–18.

3. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2005;46:e1–82.

4. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115–40.

5. Mentz RJ, Kelly JP, von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. J Am Coll Cardiol 2014;64:2281–93.

6. Geib T, Plappert N, Roth T, et al. Prevalence of sleep-disordered breathing-related symptoms in patients with chronic heart failure and reduced ejection fraction. Can J Cardiol 2015;31:839–45.

7. Costanzo MR, Khayat R, Ponikowski P, et al. Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. J Am Coll Cardiol 2015;65:72–84.

8. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. J Am Coll Cardiol 2007;49:1625–31.

9. Oldenburg O, Bitter T, Fox H, Horstkotte D. Heart failure [in German]. Somnologie 2014;18:19–25.

10. Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. Int J Cardiol 2006;106:21–8.

11. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007;9:251–7.

12. Schulz R, Blau A, Borgel J, et al. Sleep apnoea in heart failure. Eur Respir J 2007;29:1201–5.

13. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999;160:1101–6.

14. Yumino D, Wang H, Floras JS, et al. Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. J Card Fail 2009;15:279–85.

15. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001;163:608–13.

16. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med 1998;157:144–8.

17. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001;163:685–9.

18. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–5.

19. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217–39.

20. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med 2002;162:893–900.

21. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol 2007;49:2028–34.

22. Jilek C, Krenn M, Sebah D, et al. Prognostic impact of sleep disordered breathing and its treatment in heart failure: an observational study. Eur J Heart Fail 2011;13:68–75.

23. Lanfranchi PA, Braghiroli A, Bosimini E, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. Circulation 1999;99:1435–40.

24. Oldenburg O, Bitter T, Wiemer M, Langer C, Horstkotte D, Piper C. Pulmonary capillary wedge pressure and pulmonary arterial pressure in heart failure patients with sleep-disordered breathing. Sleep Med 2009;10:726–30.

25. Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation 1999;99:1574–9.

26. MacDonald M, Fang J, Pittman SD, White DP, Malhotra A. The current prevalence of sleep disordered breathing in congestive heart failure patients treated with beta-blockers. J Clin Sleep Med 2008;4:38–42.

27. Cowie MR, Mosterd A, Wood DA, et al. The epidemiology of heart failure. Eur Heart J 1997;18:208–25.

28. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.

29. Arzt M, Harth M, Luchner A, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and central sleep apnea. Circulation 2003;107:1998–2003.

30. Hastings PC, Vazir A, O'Driscoll DM, Morrell MJ, Simonds AK. Symptom burden of sleep-disordered breathing in mild-to-moderate congestive heart failure patients. Eur Respir J 2006;27:748–55.

31. Javaheri S, Caref EB, Chen E, Tong KB, Abraham WT. Sleep apnea testing and outcomes in a large cohort of Medicare beneficiaries with newly diagnosed heart failure. Am J Respir Crit Care Med 2011;183:539–46.

32. Woehrle H, Oldenburg O, Arzt M, et al. Determining the prevalence and predictors of sleep disordered breathing in patients with chronic heart failure: rationale and design of the SCHLA-HF registry. BMC Cardiovasc Disord 2014;14:46.

33. Chen H, Lowe AA, Bai Y, Hamilton P, Fleetham JA, Almeida FR. Evaluation of a portable recording device (ApneaLink) for case selection of obstructive sleep apnea. Sleep Breath 2009;13:213–9.

34. Clark AL, Crabbe S, Aziz A, Reddy P, Greenstone M. Use of a screening tool for detection of sleep-disordered breathing. J Laryngol Otol 2009;123:746–9.

35. Erman MK, Stewart D, Einhorn D, Gordon N, Casal E. Validation of the ApneaLink for the screening of sleep apnea: a novel and simple single-channel recording device. J Clin Sleep Med 2007;3:387–92.

36. Ng SS, Chan TO, To KW, et al. Validation of a portable recording device (ApneaLink) for identifying patients with suspected obstructive sleep apnoea syndrome. Intern Med J 2009;39:757–62.

37. Ragette R, Wang Y, Weinreich G, Teschler H. Diagnostic performance of single airflow channel recording (ApneaLink) in home diagnosis of sleep apnea. Sleep Breath 2010;14:109–14.

38. Wang Y, Teschler T, Weinreich G, Hess S, Wessendorf TE, Teschler H. [Validation of micro-MESAM as screening device for sleep disordered breathing]. Pneumologie 2003;57:734–40.

39. Malhotra A, Patil S, Sands S, Ayas N. Central sleep apnoea in congestive heart failure. Lancet Respir Med 2015;3:507–8.

40. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015;373:1095–105.

41. Cowie MR, Woehrle H, Wegscheider K, et al. Rationale and design of the SERVE-HF study: treatment of sleep-disordered breathing with predominant central sleep apnoea with adaptive servo-ventilation in patients with chronic heart failure. Eur J Heart Fail 2013;15:937–43.

42. Magalang UJ, Pack AI. Heart failure and sleep-disordered breathing: the plot thickens. N Engl J Med 2015;373:1166–7.

43. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3:310–8.

KEY WORDS Cheyne-Stokes respiration, heart failure, sleep apnea, sleep-disordered breathing

APPENDIX For supplemental information, please see the online version of this article.

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