Obstructive sleep apnea versus central sleep apnea: prognosis in systolic heart failure

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Background: In chronic heart failure (CHF), obstructive sleep apnea (OSA) and Cheyne-Stokes respiration (CSR) are associated with increased mortality. The present study aimed to evaluate the prognostic effect of CSR compared to OSA, in otherwise similar groups of CHF patients.

Methods: Screening for sleep-disordered breathing (SDB) was conducted among patients with CHF of New York Heart Association (NYHA) class II–IV, and left ventricular ejection fraction (LVEF) of ≤45%. The study included 43 patients (4 women) with >25% CSR during sleeping time, and 19 patients (2 women) with OSA and an apnea-hypopnea index (AHI) of ≥6. Patients were followed for a median of 1,371 days. The primary endpoint was mortality, and the secondary endpoint was combined mortality and hospital admissions.

Results: Baseline parameters did not significantly differ between groups, but CSR patients were older and had higher AHI values than OSA patients. Five OSA patients (26%) died, and 14 (74%) met the combined end-point of death or hospitalization. CSR patients had significantly higher risk for both end-points, with 23 (53%) deaths [log-rank P=0.040; HR, 2.70 (1.01–7.22); P=0.047] and 40 (93%) deaths or readmissions [log-rank P=0.029; HR, 1.96 (1.06–3.63); P=0.032]. After adjustment for confounding risk factors, the association between CSR and death remained significant [HR, 4.73 (1.10–20.28); P=0.037], hospital admission rates were not significantly different.

Conclusions: Among patients with CHF, CSR was associated with higher mortality than OSA independently of age and cardiac systolic function. CSR was also an age-independent predictor of unfavorable outcome, but hospital admission rates were not significantly different between the two groups after adjustment.

Keywords: Cheyne-Stokes respiration (CSR); chronic heart failure (CHF); obstructive sleep apnea (OSA)

Introduction

Chronic heart failure (CHF) occurs in the general population with a prevalence of 2–3% (1). CHF is linked to significant mortality, morbidity and health care costs (2).

After being diagnosed with CHF, 5 years mortality is estimated to be 50% and 10 years mortality to be 90% (3). In industrialized countries most patients with CHF are 65 years of age or over (4). CHF is predicted to be an

increasing health problem in developed countries due to increasing elderly population (5).

Sleep-disordered breathing (SDB) is a common, chronic disorder with a major impact on morbidity and mortality in the general population (6). SDB is more prevalent in patients with CHF than in any other population (7). It is estimated that up to 80% of all patients with CHF have SDB (8). The disorder is most commonly presented as either obstructive sleep apnea (OSA) or central sleep apnea, the latter often presented in a clinical form known as Cheyne-Stokes respiration (CSR) (1,6). OSA is mainly caused by nocturnal upper airway collapse, but with preserved breathing efforts during apnea periods. CSR is characterized by complete cessation of respiratory effort and airflow alternating with profound hyperventilation and crescendo-decrescendo respiratory pattern (9,10). Both types are characterized by repetitive apneas and hypopneas during sleep, accompanied by intermittent hypoxia, re-oxygenation and recurrent arousals from sleep. This may lead to activation of the sympathetic nervous system, rise in blood pressure and inflammation (11,12). Overnight sympathetic nervous activity has been found to be significantly greater in CHF patients with CSR than CHF patients with OSA (13,14). It has been argued that OSA may lead to heart failure by altered loading conditions, hypoxia and adverse impact of increased sympathetic nervous system activity (9). Some investigators speculate that CSR might represent a compensatory mechanism with protective effects in heart failure (15) while others found the rationale for treatment to be directed specifically toward CSR is based on the premise that CSR may be detrimental in itself (16).

Since SDB often is associated with CHF, and CHF is a global problem, we therefore wanted to study the impact on mortality and morbidity of OSA and CSR. We used left ventricular ejection fraction (LVEF) as a marker of CHF. We investigated the prognostic effect of OSA and CSR in a population with similar systolic function at baseline (17-19).

Methods

Study population

This was a retrospective observational study, conducted at The Hospital of Oestfold between 2007 and 2012. We initially screened 148 CHF patients (18 women) from our outpatient clinic for SDB (20). Prior to screening, we excluded patients with unstable angina, myocardial infarction in the last 3 months, coronary intervention within 3 months, cardiac surgery within 6 months, severe valvular or pulmonary disease, or thoracic myopathies. We also excluded patients who were unable to comply for any reason. All screened patients were <85 years of age, were receiving optimal heart failure medication and clinically stable during the last month prior to screening, and were in New York Heart Association (NYHA) functional class II–IV.

Measurements

A careful clinical examination was performed prior to inclusion in our outpatient clinic. Blood pressure was measured on inclusion date at standard conditions: The patients were sitting in the chair for 15 minutes before measurements. The values were obtained from right arm and only one measurement was collected for each patient. The procedure was done by an experienced nurse known to the patients. Age, gender and body weight were recorded at study start. All included patients had an LVEF of ≤45% on echocardiography measured using the modified Simpson biplane rule (21) by an independent cardiologist unaffiliated with our study. The examinations were performed on VIVID 7, GE Vingmed, Norway. Patients who were ultimately included in this study had either refused machine therapy or had used positive airway pressure (PAP) less than 3 months before enrollment.

Sleep screening

Sleep screening data were collected on an ambulatory basis in the patients' homes using polygraphy (PG) with the Embletta PDS (Embla, Corp., USA), a pocket-sized digital recorder and automatic analysis system (22,23). The Embletta has an actigraph that records activity and position. Patient position was an important channel in the scoring process. The results of automated analysis were reviewed and corrected by an independent experienced scorer, who was not connected to any commercial company or involved in patient treatment, using the applicable 2007 American Academy of Sleep Medicine (AASM) standards (24).

We determined the apnea-hypopnea index (AHI), describing the number of apnea and hypopnea episodes per hour of sleeping time. Apnea was defined as a cessation of inspiratory airflow lasting ≥10 seconds. Hypopnea was defined as either a 30% reduction in amplitude lasting ≥10 seconds, with at least a 4% decrease in saturation; or a 50%
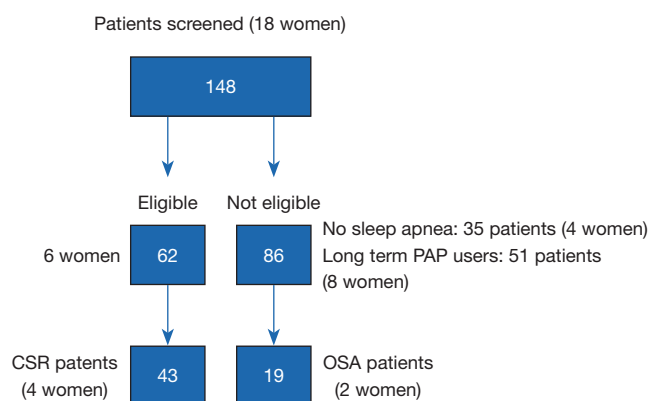
Patients screened (18 women)

148

Eligible   Not eligible

6 women   62   86   No sleep apnea: 35 patients (4 women)
                                Long term PAP users: 51 patients
                                (8 women)

CSR patents   43   19   OSA patients
(4 women)   (2 women)

Figure 1 Flow-chart showing the selection process. CSR, Cheyne-Stokes respiration; OSA, obstructive sleep apnea; PAP, positive airway pressure.

reduction in amplitude lasting ≥10 seconds, with at least a 3% decrease in saturation. Hypopneas were not scored as central or obstructive in this study. Baseline was defined as a normal breath within the vicinity of the hypopnea (24). An AHI value of 5–14 indicates mild SDB, 15–30 indicates moderate disease, and >30 indicates severe disease (6,8). For each patient, we also determined the obstructive apnea index (OAI) and central apnea index (CAI) (25), distinguished by ribcage movements and abdominal excursions. Obstructive apnea was defined as the absence of airflow and the presence of ribcage movements and abdominal excursions, whereas central apnea was defined as the absence of both airflow and of ribcage movement and abdominal excursions. CSR was defined by a minimum of three consecutive cycles of a crescendo-decrescendo pattern in the breathing signal, with periods of hyperventilation separated by central apneas and hypopneas (1). Those with a Cheyne-Stokes breathing pattern during >25% of total sleeping time were enrolled in the CSR group (n=43). Patients with an obstructive sleeping pattern, showing CSR for ≤25% of total sleeping time, and an AHI of ≥6 were included in the OSA group (n=19) (20) (*Figure 1*).

Endpoints

The primary end-point was all-cause mortality, and the secondary end-point was the combined death and readmission. End-points were determined based on information obtained from medical records and death certificates when available. For all patients, we recorded the numbers of hospitalizations and days in hospital. The

two groups were observed for a median of 1,371 (range, 904–2,104) days.

Ethics statement

The patients were originally screened for possible inclusion in a recently published study (20). All included patients gave their informed consent, and the study was approved by the local ethical committee and the Norwegian social science data services.

Statistics

Continuous variables are reported as mean ± SD or median [interquartile range (IQR)] depending on the distribution, while categorical variables are reported as number (percentage). Between-group comparisons were investigated using Fisher's exact test for categorical variables, and Student's t-test or Mann-Whitney test for continuous variables depending on the distribution. All P values were two-tailed and considered significant if ≤0.05. To evaluate the association between outcome and the presence of CSR or OSA, we used the log-rank test and univariate Cox regression. Multivariate Cox regression analysis was performed with adjustment for the following confounding risk factors: age at screening, LVEF, NYHA class ≥ III, body weight, and use of β-blockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin II (ATII) blockers.

Results

The OSA and CSR groups were comparable in terms of gender, body weight, LVEF, NYHA classification, blood pressure, and CHF medication at inclusion (*Table 1*). On average, the patients in the CSR group were 7 years older and had an AHI value that was 2.4-times higher compared to the OSA group. In both groups, the majority of patients were in NYHA functional class III, and ischemic heart disease (IHD) was the main etiology.

During follow-up, 23 CSR patients (53%) died, all men: 12 from heart failure (all had IHD), 1 from severe infection, 2 from cancer, and 8 from unknown causes (including 5 with no known illness other than ischemic heart failure). The malignancies were unknown at inclusion. In the OSA group, 5 patients died (26%), no women: 3 from heart failure due to IHD, 1 from severe infection, and 1 from unknown cause. A total of 40 patients with CSR (93%) and 14 patients with OSA (74%) met the secondary end-point

Table 1 Baseline characteristics OSA *vs.* CSR

Variables	OSA	CSR	P
N	19	43	
Age at screening	62.7±11.3	70.0±9.8	0.012*
Sex (male =1)	17 [89]	39 [91]	1.000
Body weight (kg)	85 [69–97]	82 [75–88]	0.541
Etiology			
IHD	12 [63]	31 [72]	0.555
HT	3 [16]	6 [14]	1.000
Other	4 [21]	6 [14]	0.479
Clinical			
EF (%)	30.1±6.5	28.2±7.3	0.340
NYHA 2	4 [21]	6 [14]	0.479
NYHA 3	14 [74]	35 [81]	0.513
NYHA 4	1 [5]	2 [5]	1.000
DM	6 [32]	6 [14]	0.162
SBP	120 [105–126]	120 [105–130]	0.818
DBP	75 [70–80]	70 [60–80]	0.255
Medication			
β-blocker	18 [95]	35 [81]	0.253
ACE-I	12 [63]	36 [84]	0.102
ATII-antagonist	3 [16]	5 [12]	0.692
Loop	15 [79]	35 [81]	1.000
Thiazide	0 [0]	3 [7]	0.546
Spironolactone	3 [16]	17 [40]	0.082
Digitalis	6 [32]	8 [19]	0.327
Amiodarone	2 [11]	6 [14]	1.000
Statin	11 [58]	28 [65]	0.776
Apnea indexes			
Apnea/hypopnea	10.7 (7.8–20.3)	25.4 (9.6–42.5)	0.036*
Obstructive apnea	4.5 (0.3–8.7)	1.9 (0.6–3.7)	0.109
Central apnea	0.1 (0.0–0.2)	2.6 (1.1–17.7)	0.000*
CSR (%)	0 [0–8]	51 [34–81]	0.000*

*, P≤0.050. OSA, obstructive sleep apnea; CSR, Cheyne-Stokes respiration; IHD, ischemic heart disease; HT, hypertension; DM, diabetes mellitus; EF, ejection fraction; NYHA, New York Heart Association class; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; ATII, angiotensin II; loop, loop diuretics.
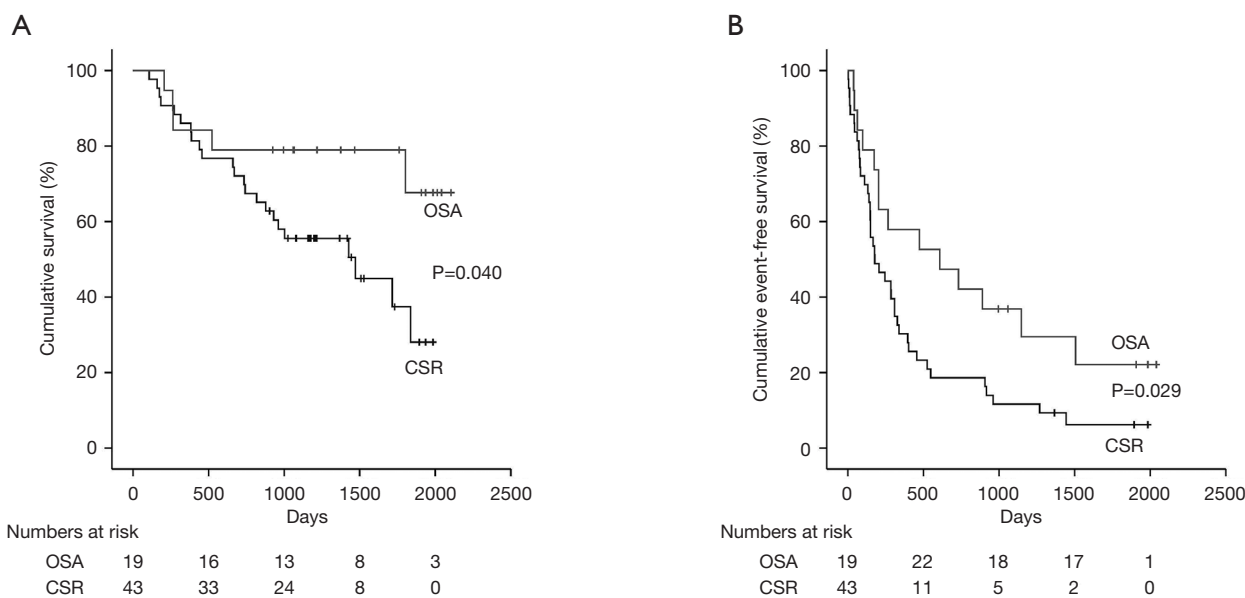
Figure 2 CSR is associated with increased risk for death and hospital admissions. Kaplan-Meier plots showing cumulative survival in percentage for death only (A) or death or readmission (B). OSA, obstructive sleep apnea; CSR, Cheyne-Stokes respiration.

of death or hospital admission during the follow-up period.

Compared to OSA, CSR was associated with a higher risk of death [CSR vs. OSA: log-rank P=0.040; HR, 2.70 (1.01–7.22); P=0.047] and of death or hospital admission [CSR vs. OSA: log-rank P=0.029; HR, 1.96 (1.06–3.63); P=0.032] during the study period (*Figure 2*). After adjustment for confounding risk factors, the association between CSR and death remained significant [HR, 4.73 (1.10–20.28); P=0.037], whereas the association between CSR and risk for death or readmission was no longer significant [HR, 2.15 (1.00–4.65); P=0.051] (*Table 2*). Compared to patients with CSR, patients with OSA needed less hospital admissions [OSA, median 2 (IQR, 0–3) vs. CSR, median 3 (IQR, 1–6); P=0.033] and hospitalization days [OSA, median 3 (IQR, 0–18) vs. median 117 (IQR, 4–33); P=0.010] (*Figure 3*).

Discussion

In this retrospective observational study, we directly compared patients with CSR and OSA, demonstrating that CSR was associated with higher mortality than OSA among CHF patients. CSR was also a marker of unfavorable outcome following adjustment for age, AHI, body weight, NYHA ≥ III, LVEF, and heart failure medication.

CHF patients with OSA also had fewer hospital readmissions than CHF patients with CSR, but the

difference was not significant after adjustment. Our study implies that among patients with heart failure, CSR is associated with worse prognosis than OSA—highlighting the importance of identifying CSR in the CHF population (26). Several prior studies have shown increased incidence of cardiovascular disease and increased mortality in CHF patients suffering from SDB compared to those without SDB (27). Nakamura *et al.* performed a meta-analysis based on 11 studies and including almost 2,000 participants with CHF, and found that patients with SDB showed significantly increased mortality risk compared to those without SDB. Moreover, they observed significantly increased mortality with CSR *vs.* no SDB, but not with OSA *vs.* no SDB (28). This is consistent with our present findings that CSR was associated with poor prognosis in CHF patients. Supplemental treating options in patients with CHF and SDB, especially in patients with CHF and CSR are limited. Though PAP treatment remains standard treatment in OSA, this treatment is of limited use in CHF with CSR and reduced systolic function (29,30).

Reduced LVEF is associated with mortality in patients with systolic heart failure (19). However, baseline LVEF did not differ between the OSA and CSR groups in our study and mortality was not different when adjusted for LVEF. Therefore, differences in systolic function due to LVEF cannot explain the higher mortality observed in the CSR

Table 2 Uni-and multivariate analyses of CSR, obstructive sleep apnea and potential confounders

Variables	Primary end-point				Secondary end-point			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
CSR/OSA	2.70 (1.01–7.22)	0.047	4.73 (1.10–20.28)	0.037	1.96 (1.06–3.63)	0.032	2.15 (1.00–4.65)	0.051
Age	1.04 (0.99–1.08)	0.090	1.03 (0.98–1.09)	0.263	1.01 (0.98–1.03)	0.665	0.99 (0.96–1.02)	0.519
Body weight	1.00 (0.98–1.03)	0.911	1.02 (0.99–1.06)	0.175	1.00 (0.97–1.01)	0.901	1.00 (0.99–1.02)	0.766
LVEF	0.96 (0.91–1.01)	0.140	0.97 (0.92–1.02)	0.235	0.99 (0.95–1.03)	0.466	0.99 (0.95–1.03)	0.572
NYHA ≥ III	1.92 (0.45–8.23)	0.382	1.03 (0.14–7.68)	0.974	1.11 (0.34–3.58)	0.866	1.30 (0.32–5.29)	0.716
ACE/ATII-inhibitor	0.76 (0.26–2.21)	0.608	0.22 (0.04–1.14)	0.071	1.33 (0.53–3.36)	0.549	0.76 (0.25–2.34)	0.631
β-blockers	0.36 (0.15–0.87)	0.023	0.39 (0.13–1.15)	0.088	0.49 (0.24–1.02)	0.057	0.55 (0.24–1.27)	0.163
AHI	1.02 (1.00–1.04)	0.137	1.00 (0.98–1.02)	0.896	1.01 (0.99–1.03)	0.284	1.00 (0.98–1.02)	0.815

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class; CSR, Cheyne-Stokes respiration; OSA, obstructive sleep apnea; ACE, angiotensin-converting enzyme inhibitor; ATII-inhibitor, angiotensin II receptor antagonist; AHI, apnea-hypopnea index.
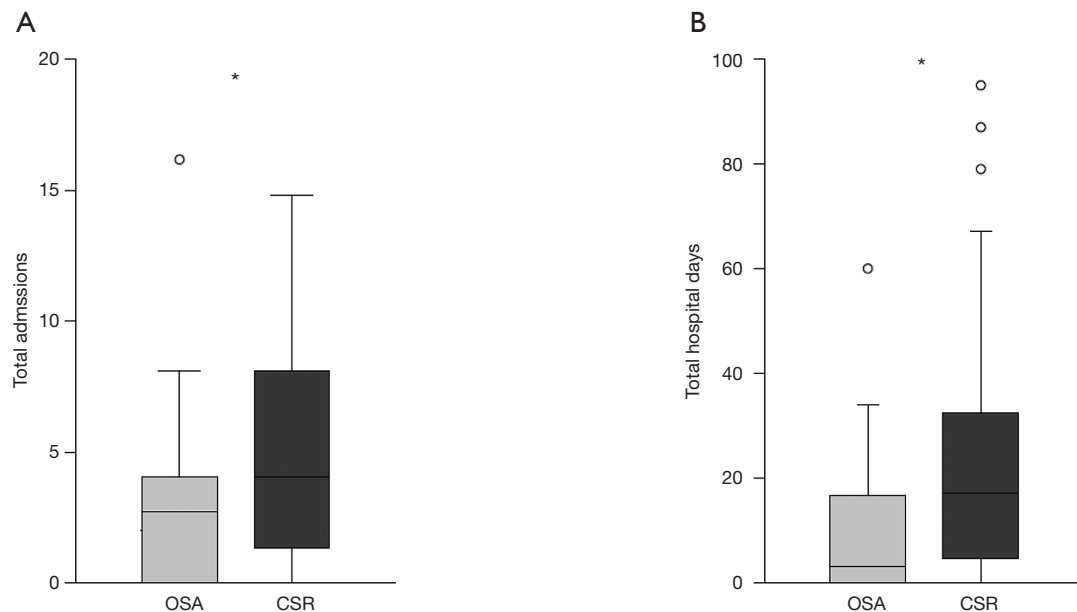

Figure 3 Patients with CSR have more hospital admissions and days in hospital than patients with obstructive sleep apnea. Box plots showing number of admissions (A) and hospital days (B). The line represents the median value, the box boundaries the 25th to 75th percentile, the whiskers 1.5 times the IQR, and the open dots outliers. *, P≤0.050. OSA, obstructive sleep apnea; CSR, Cheyne-Stokes respiration; IQR, interquartile range.

group. Moreover, the two groups did not significantly differ in NYHA functional class or in systolic or diastolic blood pressure at baseline.

Hospitalization for CHF increases with age (4). Interestingly, we found that patients with CSR were significantly older than those with OSA.

AHI was also significantly higher in CSR patients than OSA patients. This is in accordance with a prior report by Damy *et al.*, which described a steep increase in mortality for an AHI of >5 per hour sleep (31).

Factors other than AHI may also play important roles in the poor outcome in the CSR group, since we found that the worse outcome in this group persisted even with adjustment for AHI values.

Sudden death occurred in six of our patients, including five patients with CSR, most likely caused by ventricular arrhythmias. Therefore, we speculate that an increased sympathetic tone, with subsequent increased risk for arrhythmias, may be one possible mechanism underlying the higher mortality in the CSR group. Hallmarks of both OSA and CSR include hypoxia and arousals from sleep, which are associated with sympathetic nerve stimulation (32). Increased sympathetic tone and heart rate are especially harmful in patients with CHF, potentially leading to myocyte injury and functional and structural abnormalities (6). CHF patients with CSR show higher synaptic nerve activity and higher overnight urinary norepinephrine compared to CHF patients with OSA (33). In particular, severe central sleep apnea is associated with impaired autonomic control, increased arrhythmias, daytime hypocapnia and enhanced ventilator response to exercise (1,34,35).

This may partly explain why hospital admission rates were not significantly different between the two groups after adjustment. Patients with CHF and CSR often die suddenly at home and are not admitted to hospital.

SDB may promote atherosclerosis and aggravate cardiac failure (36). Obesity is reportedly also a major risk factor in men with OSA, as the condition is worsened by layering of fat adjacent to the pharynx (9). Most patients in both the CSR and OSA groups of our study had CHF due to IHD; therefore, ischemia cannot explain the different results between the groups. Additionally, the two groups did not significantly differ in weight. Pulmonary capillary wedge pressure (PCWP) is reportedly elevated in CHF patients with CSR compared to in CHF patients with OSA and in CHF patients without SDB (37). This may support the involvement of some additional unknown mechanism influencing our results.

One challenge in interpreting our results relates to the selection process. OSA and CSR can co-exist, and an overnight shift from OSA to CSR has been documented (38). Moreover, some authors hypothesize that OSA could predispose CHF patients to CSR (10). We classified SDB as obstructive or central based on the dominant sleep pattern during the night. Polysomnography (PSG) would have been preferable compared to PG but was not available at our hospital. However, the high degree of agreement between AHIs obtained from the two scoring methods suggests that PG may be used as an alternative to PSG for SBD assessment among heart failure patients (23). But lack of PSG in our study is a limitation.

Limitations

Limitations of our study include its observational nature and the small number of participants. Additionally, the group balance was not optimal, with fewer patients in the OSA group. The mean AHI in the OSA group was 10.7, categorized as mild OSA. Mild OSA has not been convincingly shown to have adverse cardiovascular consequences. The results may have been influenced by the higher AHI and age in the CSR group; however, the association between CSR and poor outcome remained significant after adjustment for several confounders, including AHI and age.

Conclusions

Our observational study revealed that CSR was associated with higher mortality and risk of hospitalization compared to OSA among patients with similar degrees of CHF. However, differences in mortality and hospitalization were not related to age, and CSR was an age-independent predictor of unfavorable outcome. Hospital admissions rates were not significantly different between the two groups after adjustment. The search for supplemental treating options in patients with CHF and SDB must continue, especially regarding CHF patients with CSR.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cdt.2020.03.02). MV reports other from License agreement with Paradigm Biopharma, outside the submitted work. In addition, MV has a patent Uses of enzyme inhibitors pending. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All included patients gave their informed consent, and the study was approved by the local ethical committee (No. 15470) and the Norwegian social science data services.

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