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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Cheyne-stokes respiration during wakefulness in patients with chronic heart failure

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Abstract

Purpose Cheyne-Stokes respiration (CSR) during sleep has been studied extensively in patients with chronic heart failure (CHF). Prevalence and prognostic significance of CSR during wakefulness in CHF, however, are largely unknown.

Methods CSR during wakefulness with an apnea-hypopnea cut-off ≥5/h and moderate to severe CSR with an apnea-hypopnea cutoff ≥15/h were analyzed using polysomnographic recordings in 267 patients with stable CHF with reduced left ventricular (LV) ejection fraction at our institution. Primary endpoint during follow-up was heart transplant-free survival.

Results Fifty of 267 patients (19%) had CSR during wakefulness and 73 of 267 patients (27%) had CSR during sleep. CSR during wakefulness was associated with advanced age, atrial fibrillation, decreased LV ejection fraction, increased LV end-diastolic diameter, brain natriuretic peptide, New York Heart Failure class, and CSR during sleep. During 43 months mean follow-up, 67 patients (25%) died and 4 patients (1%) underwent heart transplantation. Multivariate Cox analysis identified age, male gender, chronic kidney disease, and LV ejection fraction as predictors of reduced transplant-free survival. CSR during wakefulness with an apnea-hypopnea cutoff ≥5/h as well as moderate to severe CSR while awake using an apnea-hypopnea cutoff ≥15/h did not predict reduced transplant-free survival independently from confounding factors.

Conclusion CSR during wakefulness appears to be a marker of heart failure severity.

Keywords Cheyne-stokes respiration · Heart failure · Polysomnography

Introduction

Cheyne-Stokes respiration (CSR) during sleep has been reported in approximately 50% of patients with chronic heart failure (CHF) [1–19]. Many previous studies consistently showed a significant association between CSR during sleep and heart failure severity with increased neurohumoral activation, elevated brain natriuretic peptide (BNP) levels, increased pulmonary capillary wedge pressure, higher New York Heart Association (NYHA) classes and decreased left ventricular (LV) ejection fractions. The results of previous studies with regard to the prognostic significance of CSR during sleep are inconsistent. Most previous studies found CSR during sleep to be a predictor of mortality during follow-up [11, 13, 14, 16–19], whereas other studies including a large prospective study from our center found CSR during sleep to be a marker for CHF severity but not an independent predictor of outcome in patients with CHF [1, 2, 12, 15]. In contrast to CSR during sleep [1–19], only few studies investigated CSR during wakefulness in patients with CHF [20–22]. The purpose of the present study was threefold: first, to determine the prevalence of CSR during wakefulness in a large patient cohort with CHF; second, to analyze the relationship between CSR during

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wakefulness and CSR during sleep; and third, to determine the prognostic value of CSR during wakefulness with regard to reduced heart-transplant-free survival.

Methods

Patients

The study population consists of 267 patients with stable CHF who were originally enrolled in our previous study between August 2007 and June 2011 [1, 2] (Fig. 1). All patients were in a stable condition NYHA class I, II or II with left ventricular (LV) ejection fractions ≤50% by echocardiography due to ischemic or nonischemic cardiomyopathy. Patients were excluded from the study if they had one or more of the following conditions: history of sleep disordered breathing, advanced kidney disease with an estimated glomerular filtration rate <15 ml/min per 1.73 m^2 or hemodialysis, advanced liver disease, advanced respiratory dysfunction, pregnancy, malignancies, alcohol or drug abuse. The study protocol was reviewed and approved by the ethics committee of the University of Marburg. Written informed consent had been obtained from all study patients.
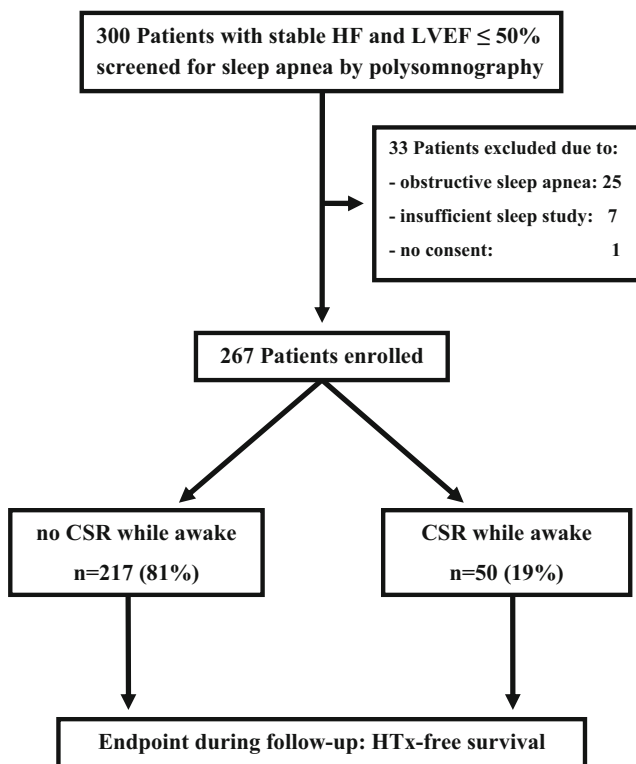

Fig. 1 Study profile of 267 enrolled patients with chronic stable systolic heart failure in New York Heart Failure class I, II or III. *CSR* indicates Cheyne-Stokes respiration, *HF* indicates heart failure, *LVEF* indicates left ventricular ejection fraction

Echocardiography

Two-dimensional echocardiographic examinations were performed in all patients using a Vingmed Vivid Seven™ machine (General Electronics Medical Systems, Solingen, Germany) to determine left atrial diameter, LV ejection fraction, and LV size. LV ejection fraction was measured in the apical four-chamber view and orthogonal two-chamber view using the disk summation method (modified Simpson's rule algorithm). All echocardiographic studies were performed by cardiologists unaware of polysomnography results.

Kidney function

Kidney function was assessed at study entry by the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula. Chronic kidney disease of at least stage 3 was diagnosed in patients with two eGFR values below 60 ml/min per 1.73 m^2 with an interval of at least 3 months.

Polysomnography

Unattended cardiorespiratory polysomnography at study entry was performed using Somnocheck R&K™ instruments (Weinmann, Hamburg Germany) in each patient in our hospital in a regular bedroom outside of the sleep laboratory. The Somnocheck 2 R&K device was applied by certified sleep technicians at 10 p.m. and was removed in the next morning at approximately 7 a.m. by another sleep technician. Wake time was determined exclusively based on continuous electroencephalographic monitoring throughout polysomnography (Fig. 2). Total wake time included wake time before lights out, wake time after lights out, and wake time after lights on. Since polysomnography was performed unattended in a regular bedroom outside of the sleeping laboratory, lights out and lights on times were not recorded. All polysomnography recordings were stored on an integrated, interchangeable compact flash card and were digitally converted to European Data Format. CSR was visually scored by two experienced technicians with the sleep technician's scoring being over read by a board certified sleep medicine physician according to the recommendations of the American Academy of Sleep Medicine (AASM) [23] as previously described in detail [1]. All CSR analyses were performed by sleep technicians and a sleep medicine physician, all of whom were unaware of the patients' clinical conditions and outcome. CSR during sleep as well as during wakefulness was diagnosed from polysomnographic recordings according to the updated AASM criteria [24]. A respiratory event was scored as Cheyne-Stokes breathing if both of the following criteria were met: (1)
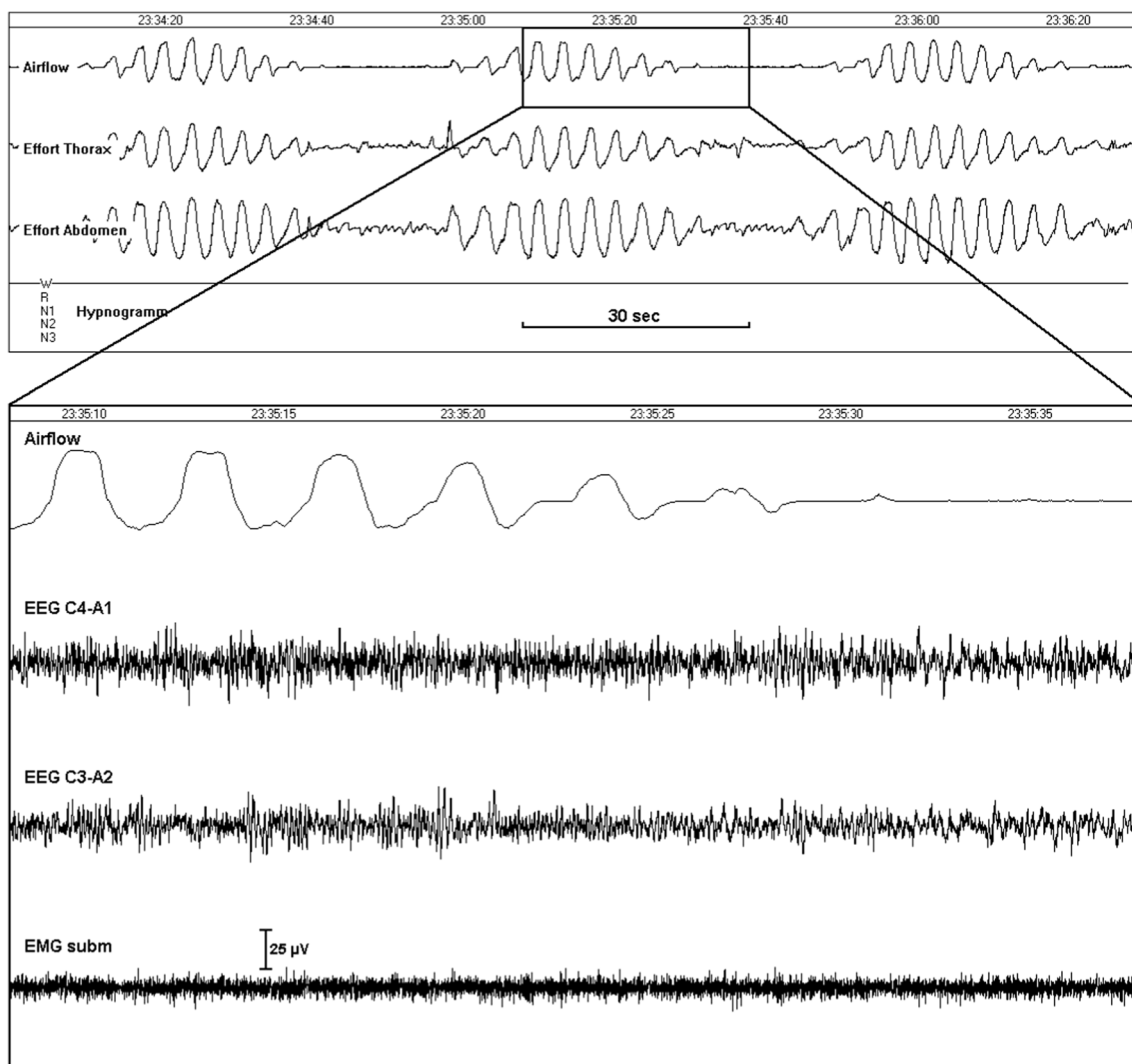
Fig. 2 Polysomnography showing CSR while awake. The top section provides respiratory signals and the corresponding hypnogram. Airflow was measured using a nasal cannula while effort was derived by piezoelectric tension belts. The lower section shows a 30-s period of the EEG derived from the positions C4 and C3 as well as submental chin electromyogram (EMG). The electroencephalogram (EEG) exhibits a spectrum typical for wakefulness with prevailing alpha- and beta-frequency components. The EMG tonus of about 12 µV also indicates wakefulness consistent with the EEG pattern

the presence of episodes of at least three consecutive central apneas and/or central hypopneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 s, and (2) presence of at least five central apneas and/or central hypopneas per hour associated with the crescendo/decrescendo breathing pattern recorded over at least 2 h of monitoring. Cheyne-Stokes apneas were classified if the duration between two adjacent breaths was at least 10 s. Cheyne-Stokes hypopneas were marked if the amplitude fell below 70% of the baseline amplitude for at least 10 s. For the purpose of the present study, all CSA events which did not meet AASM criteria for CSR were excluded as previously described [2]. Patients with a history of sleep apnea and patients with obstructive sleep apnea with an apnea/hypopnea index ≥5/h had been excluded from study participation. Therefore, the obstructive apnea/hypopnea index during polysomnography from 10 p.m. to 7 a.m. was only 0.6 ± 1.9/h.

Follow-up

Follow-up started at the time of polysomnography and ended in December 2013 [1]. Primary endpoint was all-cause mortality or the need for heart transplantation. Initiation of ventilation therapy was discouraged by the study protocol because we sought to investigate the prognostic significance of CSR in untreated patients and because ventilation therapy has not been proven to improve survival in HF patients with CSA [25, 26]. Due to the attending physician's wish or the patient's

wish, however, eight of 267 study patients (3%) received either continuous positive airway pressure ventilation or adaptive servo ventilation during follow-up.

Statistical analysis

Baseline clinical characteristics between patients with and without CSR during wakefulness using a CSR index cutoff ≥5/h were compared using the Jonckheere-Trepsta-Trend test for continuous variables, Cochran-Armitage-trend test for nominal variables, and Kendall's Tau-b test for ordinal variables. Univariate and multivariate Cox regression analysis was used to evaluate the association between baseline variables as listed in Table 2 and heart-transplant-free survival as predefined outcome measure. The final Cox regression model was built by a stepwise procedure, with a cut-off level of 0.20 for entry into the model. Event-free survival probabilities were estimated with the Kaplan-Meier method. Our study had a power of 79% to detect a 100% increase in mortality or heart transplant during follow-up in patients with a CSR index ≥5/h compared to patients with a CSR index <5/h during wakefulness. In order to evaluate the prognostic significance of moderate or severe CSR during wakefulness, univariate and multivariate Cox analyses were repeated using a CSR index cutoff ≥15/h. Our study had a power of 45% to detect a 100% increase in mortality or heart transplant during follow-up in patients with a CSR index ≥15/h compared to patients with a CSR index <15/h during wakefulness. Results are expressed as mean ± standard deviation unless specified otherwise. All probability values reported are two-sided, and a probability value of $P < 0.05$ was considered to indicate statistical significance. R-software version 3.02 (www.R-project.org) and package survival was used for all statistical analyses.

Results

Characteristics of 267 study patients

The clinical characteristics of the 267 study patients are summarized in Table 1. Unattended polysomnography was performed from 10 p.m. until approximately 7 p.m. for 512 ± 43 min (range: 360–599 min). Duration of wake time during polysomnography, which was determined exclusively by electroencephalography in each patient, was 222 ± 96 min with a median wake time of 215 min and a wide range of wake time from 45 to 514 min. CSR with a CSR apnea-hypopnea index ≥5/h was present in 50 of 267 patients (19%) during wakefulness and in 73 of 267 patients (27%) during sleep ($P < 0.001$). CSR during wakefulness with a CSR apnea/hypopnea index ≥5/h was significantly associated with advanced age, atrial fibrillation, decreased left ventricular (LV) ejection fraction, increased LV end-diastolic diameter, brain

natriuretic peptide, and New York Heart Failure (NYHA) class. Thirty-five patients (13%) had only mild CSR during wakefulness with a CSR apnea-hypopnea index ≥5/h and <15/h. Fifteen patients (6%) had moderate CSR during wakefulness with a CSR apnea-hypopnea index ≥15/h and <30/h, and no patient had severe CSR during wakefulness with a CSR apnea-hypopnea index ≥30/h.

Predictors of reduced heart transplant-free survival

During 43 ± 18-months mean follow-up, 67 patients (25%) died and 4 patients (1%) underwent heart transplantation (Table 2). On univariate analysis, transplant-free survival was associated with younger age, female gender, absence of diabetes mellitus, chronic kidney disease and atrial fibrillation, preserved LV ejection fraction, nonischemic cardiomyopathy, lower brain natriuretic peptide, absence of diuretics, and absence of CSR during wakefulness using a CSR index cutoff ≥5/h. Use of ICDs or cardiac resynchronization devices as well as use of heart failure medication including ACE inhibitors, angiotensin receptor blockers, ß-blockers, and aldosterone antagonists were similar in patients with and without transplant-free survival during follow-up. Multivariate Cox analysis identified age, male gender, chronic kidney disease, and decreased LV ejection fraction, but not CSR during wakefulness with a CSR hypopnea/apnea index cutoff ≥5/h as well as moderate to severe CSR with a CSR hypopnea/apnea index cutoff ≥15/h, as predictors of reduced transplant-free survival (Table 2 and Fig. 3).

Discussion

To the best of our knowledge, this is the first study to assess the prognostic significance of CSR during wakefulness in more than 100 patients with CHF. There are three main findings of our present study. First, CSR occurred significantly less often during wakefulness compared to sleep. Second, CSR during wakefulness was marker of heart failure severity with significantly decreased LV ejection fraction, increased brain natriuretic peptide, higher NYHA functional heart failure class, and, in addition, advanced age. Third, CSR during wakefulness did not predict reduced transplant-free survival after adjustment for confounding variables by multivariate Cox analysis including age, male gender, chronic kidney disease, and decreased LV ejection fraction.

In contrast to CSR during sleep, which has been studied extensively in patients with CHF, only three previous studies examined the prevalence and prognostic significance of CSR during wakefulness in more than 50 patients [20–22]. Ponikowski et al. [20] analyzed breathing patterns during wakefulness in 74 stable CHF patients. Whereas polysomnography at nighttime from 10 p.m. to 7 a.m. was used to detect CSR

Table 1 Presenting characteristics stratified for the presence of CSR while awake

Baseline characteristics	All patients	No CSR while awake	CSR while awake	P
Patients, n (%)	267 (100)	217 (81)	50 (19)	
Age, years	60 ± 14	59 ± 14	67 ± 10	<0.001
Men, n (%)	201 (75)	159 (73)	42 (84)	0.160
Body mass index, kg/m²	28 ± 5	28 ± 5	28 ± 6	0.920
Diabetes mellitus, n (%)	75 (28)	55 (25)	20 (40)	0.057
Chronic kidney disease, n (%)	84 (31)	64 (29)	20 (40)	0.203
Atrial fibrillation	70 (26)	49 (23)	21 (42)	0.008
Left bundle branch block	50 (19)	43 (20)	7 (14)	0.454
Echocardiogram				
LV ejection fraction, %	34 ± 10	34 ± 10	31 ± 9	0.019
LV end-diastolic diameter, mm	61 ± 9	61 ± 9	64 ± 8	0.015
Underlying heart disease, n (%)				
Ischemic cardiomyopathy	124 (46)	95 (44)	29 (58)	0.097
Nonischemic cardiomyopathy	143 (54)	122 (56)	21 (42)	
Brain natriuretic peptide[a]	685 ± 852	618 ± 826	964 ± 909	0.019
NYHA heart failure class, n (%)				
Class I	39 (15)	34 (16)	5 (10)	0.048
Class II	99 (37)	86 (40)	13 (26)	
Class III	129 (48)	97 (44)	32 (64)	
ICD, n (%)				
Single or dual chamber ICD	86 (32)	63 (29)	23 (46)	0.069
CRT-ICD	34 (13)	29 (13)	5 (10)	
Medication, n (%)				
ACE inhibitors or ARBs	177 (66)	145 (67)	32 (64)	0.830
Diuretics	194 (73)	155 (71)	39 (78)	0.445
Aldosterone antagonists	105 (39)	89 (41)	16 (32)	0.310
ß-blockers	211 (79)	174 (80)	37 (74)	0.438

[a] available in 251 patients

during wakefulness in our study, Ponikowski et al. [20] used power spectral analyses applied to 30-min recordings of respiration between 9 and 12 a.m. using a plethysmography to detect cyclical breathing. In addition, Ponikowski et al. [20] analyzed peripheral chemosensitivity and heart rate variability as well as baroreflex sensitivity as indices of autonomic tone. Cyclic breathing during wakefulness in the study by Ponikowski et al. [20] was found in 66% of patients including periodic breathing with apneas in 30% of patients and periodic breathing without apneas in another 36% of patients. Cyclical breathing with our without apneas was associated with more heart failure symptoms, impaired autonomic balance, and increased peripheral chemosensitivity [20]. Multivariate analysis revealed that cyclical breathing during wakefulness predicted poor 2-year survival independent of peak O_2 consumption and NYHA class [20]. The 2-year survival was 67% for patients with cyclical breathing during wakefulness compared to 96% for patients without cyclical respiratory breathing during wakefulness [20].

The second study by Brack et al. [21] investigated the circadian prevalence of CSR and its influence on survival in 60 ambulatory patients with stable CHF. Similar to the findings of our study, Brack et al. [21] found a significantly higher CSR prevalence during sleep of 62% compared to CSR during wakefulness of 16% using ≥15 periodic breathing cycles as cutoff to define CSR. Importantly, the study of Brack et al. [21] differs from our study in several important aspects. First, Brack et al. [21] recorded the circadian breathing pattern during 24 h with a portable monitoring device including a respiratory inductive plethysmograph which allowed for prospective analysis of the complete circadian CSR prevalence in heart failure patients outside the sleep laboratory, whereas we retrospectively analyzed CSR during periods of wakefulness during polysomnography at nighttime between 10 p.m. until 7 a.m. with a potential increase in pulmonary congestion in the supine position at nighttime [27] compared to a predominantly upright position during daytime. Therefore, our study does not provide any data with regard to the prevalence and prognostic significance of CSR during wakefulness at daytime. Secondly, the prevalence of moderate to severe CSR during wakefulness as indexed by a CSR index ≥15/h was much lower in our study (6%) compared to the study by Brack et al. [21], who found a prevalence of 16% for CSR using an index ≥15/h

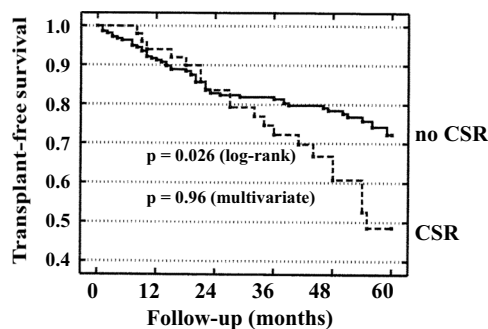**Table 2** Predictors of transplant-free survival

Baseline characteristics	All patients ($n = 267$)	Survival ($n = 196$)	Death/htx ($n = 71$)	P Univ.	P Multiv..	HR (95% CI)
Age, years	60 ± 14	58 ± 14	67 ± 13	<0.001	0.006	1.03 (1.01–1.06)
Male gender, n (%)	201 (75)	138 (70)	63 (89)	0.002	0.005	2.87 (1.37–6.06)
Body mass index, kg/m^2	28 ± 5	28 ± 5	27 ± 6	0.714		
Diabetes mellitus, n (%)	75 (28)	48 (24)	27 (38)	0.043		
Chronic kidney disease, n (%)	84 (31)	44 (22)	40 (56)	<0.001	0.004	2.17 (1.29–3.67)
Atrial fibrillation	70 (26)	43 (22)	27 (38)	0.007		
Left bundle branch block	50 (19)	40 (20)	10 (14)	0.224	0.19	0.63 (0.32–1.25)
LV ejection fraction, %	34 ± 10	35 ± 10	30 ± 10	<0.001	0.008	0.97 (0.94–0.99)
LV end-diastolic diameter, mm	61 ± 9	61 ± 9	62 ± 9	0.246		
Ischemic cardiomyopathy	124 (46)	79 (40)	45 (63)	0.001		
Nonischemic cardiomyopathy	143 (54)	117 (60)	26(37)			
Brain natriuretic peptide[a]	684 ± 851	486 ± 623	1229 ± 1123	<0.001		
Diuretics	194 (73)	131 (67)	63 (89)	<0.001	0.14	1.77 (0.83–3.80)
NYHA class I	39 (15)	33 (17)	6 (8)	0.152		
NYHA class II	99 (37)	73 (37)	26 (37)			
NYHA class III	129 (48)	90 (46)	39 (55)			
Ventilation therapy, n (%)	8 (3)	7 (4)	1 (1)	0.388		
CSR while awake, n (%)						
CSR index ≥5/h	50 (19)	30 (15)	20 (28)	0.026	0.96	1.02 (0.59–1.74)
CSR index ≥15/h	15 (6)	9 (5)	6 (8)	0.363	0.646	0.82 (0.35–1.93)

[a] available in 251 patients

while awake. This difference in CSR prevalence between both studies may be explained by the presence of more advanced heart failure in the population studied by Brack et al. [21]. Mean LV ejection fraction was as low as 26.5% in the study by Brack et al. [21] compared to a much higher mean LV

Fig. 3 Kaplan Meier estimates for transplantation-free survival of 267 study patients stratified for patients with CSR versus without CSR using a CSR index cutoff ≥5/h. Univariate analysis using the log-rank test showed a significantly decreased survival for patients with versus without CSR while awake ($P = 0.026$). Multivariate Cox regression analysis, however, revealed no significant difference in transplant-free survival between patients with versus without CSR while awake after adjustment for potential confounding factors as summarized in Table 2 (HR 1.02; 95% CI: 0.59–1.74; $P = 0.96$)

ejection fraction of 34% in our study. In contrast to our study, Brack et al. [21] found CSR during wakefulness to be an independent predictor of mortality during follow-up with a hazard ratio of 3.8.and a wide 95% confidence interval of 1.1 to 12.7. This wide confidence interval may be explained by the relatively small number of 60 patients and the relatively small number of 13 endpoints during follow-up in the study by Brack et al. [21].

The third study by Silva et al. [22] performed polysomnography at nighttime in 89 consecutive patients with systolic heart failure NYHA 1 to 4. Silva et al. [22] were able to analyze CSR during wakefulness before sleep onset in 75 of these 89 patients and diagnosed CSR when at least 80% of apnea or hypopneas episodes were central apneas or hypopneas with an apnea/hypopnea index >15/h [22]. As a result, Sylva et al. [22] found CSR while awake in 35% of 75 patients with CHF before sleep onset. During 25 months mean follow-up, 22 patients with CHF died. Similar to the results of our study, univariate analysis revealed a significantly higher mortality during follow-up in patients with CSR versus without CSR during wakefulness in study by Silva et al. [22], whereas multivariate Cox analysis failed to show a significant association between CSR during wakefulness and mortality independently of confounding variables. Of note, the study by Silva et al. [22] differs from our study in several important aspects. First, the most important predictor of mortality was

NYHA class 4 heart failure in the study by Silva et al. [22], whereas patient with NYHA class 4 heart failure were excluded from study participation in our study, since we sought to determine the clinical significance of CSR during wakefulness in chronic stable systolic heart failure. Furthermore, Silva et al. [22] included patients with obstructive sleep apnea, whereas patients with more than five obstructive sleep apneas or hypopneas per hour were excluded in our study. Finally, many patients in the cohort of Silva et al. [22] suffered from Chagas disease, whereas no patient in our cohort had Chagas disease.

Study limitations

CSR during wakefulness was analyzed retrospectively from polysomnographic recordings of a previous study at our center [1] with all potential inherent limitations of retrospective analyses. To avoid an investigator bias, however, all analyses of polysomnographic recordings were performed by two sleep technicians and over read by a sleep medicine physician, all of whom were unaware of the patients' clinical conditions and outcome. Although wakefulness was confirmed using electroencephalographic recordings during polysomnography in all patients, we studied patients only at nighttime between 10 p.m. and 7 a.m. predominantly in the supine position, which may have influenced the prevalence of CSR in our patient population with CHF due to increased pulmonary congestion in the supine position [27]. Since we excluded patients with advanced heart failure NYHA class 4, who have been found to have the highest prevalence of CSR during wakefulness, we cannot draw any conclusions with regard to this important group of heart failure patients. In addition, we excluded patients with heart failure and preserved LV ejection fraction. Finally, the power of our study was only 45% to detect a 100% increase in mortality or heart transplant during follow-up in patients with a CSR index ≥15/h compared to patients with a CSR index <15/h during wakefulness, and no patient in our study had severe CSR during wakefulness with a CSR index ≥30/h. Therefore, we cannot draw any final conclusions with regard to moderate or severe CSR during wakefulness as a risk factor for transplant-free survival in patients with stable systolic heart failure.

Conclusion

In patients with stable systolic CHF, CSR during wakefulness is found less often than CSR during sleep and appears to be marker for CHF severity. In our selected patient population with chronic stable systolic heart failure, CSR during wakefulness did not predict transplant-free survival independently from confounding factors. Our findings do not support the hypothesis that patients with CHF and CSR during wakefulness might benefit from ventilation therapy.

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