

Cheyne-Stokes Respiration and Prognosis in Modern-Treated Congestive Heart Failure

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Abstract In patients with congestive heart failure (CHF), a high prevalence of sleep-disordered breathing has been described. Cheyne-Stokes respiration (CSR) is present in up to 40% of patients with CHF. During the last decade, the medical treatment has been substantially improved. This study was designed to analyze the prognosis of CSR in modern-treated patients with CHF. For this purposes, in 57 patients with CHF who received modern treatment, a 5-year follow-up after initial full night polysomnography was performed. The mean follow-up period was 38 ± 18 months. Mean age was 62 ± 13 years and the mean ejection fraction was 25 ± 7 percent. Respiratory polygraphy revealed CSR with a respiratory disturbance index >5 per hour of sleep in 39 of 57 patients. Twelve patients died. CSR was only characterized by a tendency of worsening (log-rank test, $p = 0.25$). However, there was a significant difference toward positive outcome for patients who received cardiac resynchronization therapy (log-rank test, $p = 0.036$). Using Multivariate Cox's proportional hazard regression with the factors resynchronization and CSR, the effect of resynchronization was almost significant ($p = 0.08$). In conclusion, no significant change of Cheyne-Stokes prevalence can be found in our small group of modern-treated patients with

CHF. Cardiac resynchronization therapy was associated with improved patient outcome.

Keywords Cheyne-Stokes respiration · Chronic heart failure · Prognosis · Cardiac · Resynchronization therapy

Introduction

Congestive heart failure is one of the leading causes of morbidity and mortality in developed countries. In recent years, there has been a high prevalence of sleep-disordered breathing in patients with congestive heart failure [1–4]. Since the description of waxing and waning breathing pattern by Cheyne and Stokes, the occurrence of Cheyne-Stokes respiration is well recognized in congestive heart failure [5, 6]. Several investigators have shown an increased mortality in congestive heart failure combined with Cheyne-Stokes respiration [7–9]. Possibly this is based on an increased neurohumoral stress on the heart [10]. The treatment of patients with congestive heart failure has changed during the last decade as new therapeutic standards, such as beta-blockers and angiotensin-converting-enzyme inhibitors, have been established [11, 12]. The prognosis for patients with congestive heart failure could be substantially improved by these.

Recent investigations have focused on changes in prevalence of sleep-breathing disorders. In 203 German patients with congestive heart failure and left ventricular ejection fraction $<40\%$, an apnea-hypopnea index cutoff of approximately 10 per hour were seen by polygraphy in 71% with a majority in obstructive sleep apnea probably due to higher body mass index [13]. In a retrospective analysis in 450 consecutive patients with congestive heart failure with

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an apnea-hypopnea index cutoff of approximately 10 per hour, Sin et al. found a prevalence of sleep-disordered breathing of 72% [14]. In this retrospective analysis, the prevalence of Cheyne-Stokes respiration with 33% was comparable to the German patients with 28% [13]. In contrast, the prevalence of sleep-disordered breathing according to common study criteria with an apnea-hypopnea index cutoff of approximately 10 per hour in 81 patients with congestive heart failure has been approximately 50% [1]. The differences compared to the findings of Javaheri et al. are possibly the result of a higher body mass index, leading to an increased prevalence of obstructive sleep apneas. Furthermore, there was no predefined inclusion or exclusion fraction in Sins' patient collective.

However, if there is a reduction of CSR and an impact of CSR on prognosis, we would expect a reduction of mortality in modern-treated congestive heart failure. This could even be forced by a new treatment option, such as cardiac resynchronization therapy, with proven influence on prevalence of CSR [15].

This study was designed to analyze the prognosis of sleep-disordered breathing, such as Cheyne-Stokes respiration, in patients suffering from modern-treated congestive heart failure.

Methods

All patients admitted to the internal medicine department at our University Hospital with heart failure were eligible if they met the following criteria: left ventricular ejection fraction $\leq 35\%$, and at least one episode of cardiac decompensation in the patient's history. They all had to be in stable cardiac conditions at NYHA-classification class 2–3 with no episode of decompensation at least during the last 6 weeks. Most patients were outpatients, but also inpatients with stable cardiac conditions were eligible. All of them had to have a beta-blocker and an angiotensin-converting-enzyme inhibitor or an angiotensin-II-antagonist as standard medication. No primary lung dysfunction with a forced expiratory volume in 1 second $< 65\%$ was accepted for participants, and no myocardial infarction should have been occurred during the last 6 months. The minimum age for patients was 18 years.

All patients provided informed consent to participate in the study, which was performed in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee at the University of Goettingen.

Polysomnography was performed in one night at the sleep laboratory of the cardiology and pneumology department during 2003–2004. No patient had a known history of sleep-disordered breathing before our investigations. To determine the stages of sleep, an electroencephalogram, a

chin electromyogram, and an electrooculogram were obtained. Thoracoabdominal excursions were measured with electrodes placed on the rib cage and abdomen. Airflow was monitored with thermocouples. All polysomnographic data were collected by computer system (Alice 4, Heinen & Löwenstein, Germany). According to the criteria of the American Academy of Sleep Medicine, there had to be at least three cycles of crescendo and decrescendo change in breathing amplitude and five or more central sleep apneas or hypopneas per hour of sleep to be scored as Cheyne-Stokes respiration [16]. Furthermore, according to common study criteria, the apnea-hypopnea index (AHI) of > 10 per hour was defined as relevant.

Statistical analysis was performed with Statistica (GmbH Software, Germany). The Mann–Whitney test was used to assess differences between patients with and those without sleep-disordered breathing, and chi-square analysis was used to analyze proportions. Kaplan–Meier plots and log-rank test were performed for mortality with censored patients due to transplantation or end of follow-up time. Finally, multivariate Cox's Proportional Hazard Regression was used to assess the effect of CSR and biventricular pacing on survival status including age, gender, and cardiac cachexia. $P < 0.05$ was considered to indicate statistical significance. Values are reported as mean \pm standard deviation.

Results

Fifty-seven patients were included in the study (Table 1); 24 patients had a dilated and 4 had a hypertrophic nonobstructive, whereas 29 had an ischemic cardiomyopathy. During follow-up, 12 patients died and 4 received cardiac transplantation. No patient was lost to follow-up. Five of the 9 women and 34 of the 48 men had CSR. Only three men had predominant obstructive sleep-breathing disorders.

Beta-blocker-medication was given to all 57 patients, and 48 were treated with angiotensin-converting-enzyme inhibitor, whereas 9 had angiotensin-II-antagonists. All patients had diuretic medications, and 17 were treated with digitalis. Twenty patients received an aldosterone antagonist. Ongoing amiodarone treatment could be evaluated in 14 patients.

According to the mentioned AASM criteria, eight patients had an AHI of < 5 per hour. If common criteria from sleep investigations were used, there would have been 22 patients (44%) with an AHI of < 10 per hour. Sleep-breathing disorders defined by a respiratory disturbance index (RDI) of > 5 per hour were seen in 74% of our patient group; 68% of all study patients had Cheyne-Stokes breathing patterns (Table 2).

Follow-up lasted for 38 ± 18 months, and no patient was lost to follow-up. For all patients included in our analysis, the mortality tended to be lower in CSR patients

Table 1 Clinical data of the patients

Variable	Patients (<i>n</i> = 57)	CSR (<i>n</i> = 39)	NCSR (<i>n</i> = 18)	<i>P</i> value
Age (yr)	62.4 ± 12.8	61.9 ± 13.7	63.3 ± 10.9	NS
Height (cm)	174.8 ± 9.5	176.7 ± 9.5	170.8 ± 8.4	<0.05
Body mass index (kg/ m ²)	26.4 ± 4.2	25.9 ± 3.7	27.3 ± 5.1	NS
Ejection fraction (%)	25.3 ± 6.5	25 ± 6	26 ± 7	NS
LVED (mm)	64.4 ± 8.3	66 ± 7	61 ± 10	<0.05
VO ₂ max (ml/min/kg)	12.4 ± 4.1 (<i>n</i> = 30)	13.3 ± 4.3 (<i>n</i> = 20)	10.5 ± 3.1 (<i>n</i> = 10)	0.1

CSR patients with Cheyne-Stokes respiration according to AASM-criteria, NCSR non-Cheyne-Stokes Respiration patients; NS not significant, LVED left ventricular end-diastolic diameter; VO₂max = peak oxygen consumption

Table 2 Characteristics of the patients during sleep

Variable	CSR (<i>n</i> = 39)	NCSR (<i>n</i> = 18)	<i>P</i> value
Total sleep time (min)	315 ± 64	288 ± 100	NS
Non-REM (min)	278 ± 56	256 ± 79	NS
REM (min)	53 ± 26	46 ± 32	NS
RDI (/h TST)	26 ± 15	12 ± 20	<0.00005
AHI (/h)	22 ± 13	10 ± 19	<0.00005
Apnea index (/h sleep)	12 ± 13	7 ± 18	<0.0005
Arousal index (/h sleep)	25 ± 13	31 ± 19	NS
Mean oxygen saturation (%)	90 ± 4	90 ± 3	NS
Minimum oxygen saturation (%)	81 ± 7	84 ± 8	NS

CSR patients with Cheyne-Stokes respiration according to AASM criteria, NCSR non-Cheyne-Stokes respiration patients, TST total sleep time, REM rapid eye movement sleep, RDI respiratory disturbance index, AHI apnea-hypopnea index, NS not significant

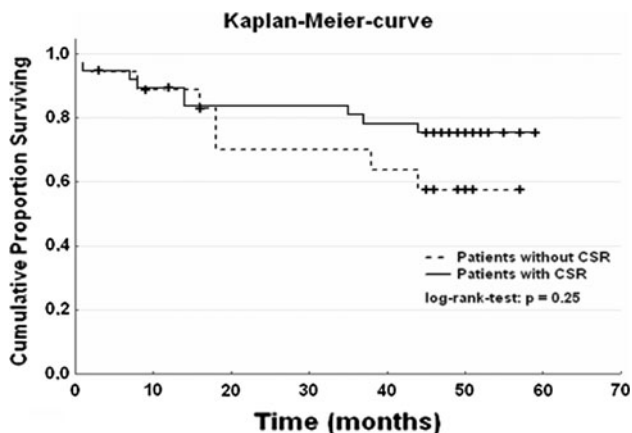


Fig. 1 Cumulative proportion surviving for all patients. CSA = Cheyne-Stokes respiration; time = months; log-rank test, $p = 0.25$

than in non-CSR patients without statistical significance (log-rank test, $p = 0.25$; Fig. 1). Neither age nor sex showed a significant difference in both groups.

In a smaller group of 35 patients without biventricular pacing, the mortality was 6 of 15 (40%) in non-CSR and 7 of 20 (35%) in CSR patients group. Figure 2 shows the cumulative proportion that survived (log-rank test, $p = 0.42$).

Comparison of patients with versus without cardiac resynchronization therapy revealed a significant difference in mortality (log-rank test, $p = 0.036$; Fig. 3). In the multivariate Cox's proportional hazard regression, the

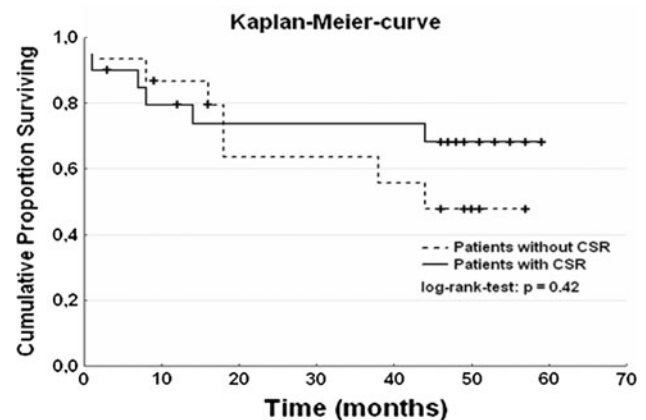


Fig. 2 Mortality in 35 patients without biventricular pacing. CSA = Cheyne-Stokes respiration; time = months; log-rank test, $p = 0.42$

combination of CSR and cardiac resynchronization therapy could only show a tendency for positive influence of resynchronization (hazard ratio, 0.32; 95% confidence interval, 0.09–1.16; $p = 0.08$).

Discussion

Cheyne-Stokes respiration is a common sleep-breathing disorder in patients with congestive heart failure [1–4]. Previous studies also have documented poorer prognosis

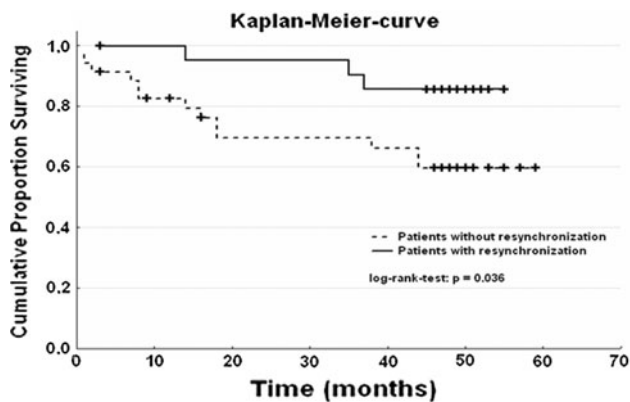


Fig. 3 Mortality in patients with versus without biventricular pacing. Bivent = cardiac resynchronization therapy (0 = without, 1 = with); time = months; log-rank test, $p = 0.036$

for this study population [7–9]. Modern medical treatment has a prognostic impact for patients with congestive heart failure [11, 12, 17, 18].

In a small study population of eight patients, Walsh and colleagues showed a reduction of apneic episodes as well as arousals and an increase of slow wave and REM sleep by treatment with captopril [19]. The prevalence of sleep-disordered breathing according to common study criteria with an apnea-hypopnea index cutoff of approximately 10 per hour in a historic collective of Javaheri et al. has been approximately 50% [1]. Still in that earlier investigation, no standard medical treatment was given as recommended by modern heart failure treatment guidelines [17]. As reported at the beginning, other investigators found a decline in prevalence by polygraphic investigation [13].

The strongest effect of modern treatment of congestive heart failure and prevalence of CSR was seen in cardiac resynchronization therapy [15]. Treatment reduction of CSR as well as an association of CSR reduction with improved sleep quality and quality of life was evident in 42 patients with heart failure by Skobel et al. [20]. A reduction in mortality for patients with congestive heart failure was described in the meta-analyses by Rivero-Ayerza et al. [21]. In our study population, this reduction in mortality during a 5-year follow-up also was shown ($p < 0.04$). However, no clear evidence for an association with CSR could be established from our data. Probably due to small sample size, the benefit of cardiac resynchronization showed only a tendency ($p = 0.08$). Furthermore, sleep investigations during follow-up for analysis of CSR reduction due to implantation of resynchronization aggregates were not obtained.

Conclusions

There appears to be no prognostic benefit for the modern medical treatment in association with CSR, although

improved prognostic outcome in congestive heart failure is known. For nonpharmacologic treatments, such as cardiac resynchronization therapy, a tendency toward a beneficial influence in CSR and a significant benefit for all patients with congestive heart failure receiving resynchronization is shown. Further clinical studies have to prove this hypothesis of a significant correlation between CSR reduction and outcome in patients with congestive heart failure.

Competing interests The authors declare to have no competing interests.

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