Risk factors and prognostic value of daytime Cheyne–Stokes respiration in chronic heart failure patients

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Abstract

Background: Sleep-related Cheyne–Stokes (CS) respiration is a known phenomenon in chronic heart failure (CHF). We aimed to study the prevalence, clinical correlates, risk factors and prognostic relevance of daytime CS, as well as its relation with neurohormonal derangement.
Methods: One hundred forty seven CHF patients with left ventricular systolic dysfunction (age: 64 ± 12 years, ejection fraction, EF, $31 \pm 8\%$, mean $\pm$ SD) underwent morning polygraphic recording, in addition to comprehensive clinical and neurohormonal evaluation.
Results: Daytime CS was detected in 87 patients (59%), and associated with worse NYHA class (2.6 ± 0.7 vs 2.2 ± 0.8, $P < 0.05$), lower EF (29 ± 8 vs $33 \pm 8\%$, $P < 0.05$), peak oxygen consumption (11.3 ± 8.3 vs 13.4 ± 4 mL/min/kg, $P < 0.05$), resting carbon dioxide level (33.1 ± 4.2 vs 37.9 ± 3.8 mm Hg, $P < 0.001$), higher norepinephrine [588 (395–939) vs (331–681) ng/L, median (interquartile range) $P < 0.01$] and natriuretic peptides [ANP: 136 (57–230) vs 66 (18–103); BNP: 284 (99–510) vs 64 (21–202); NT-proBNP: 2575 (814–3320) vs 448 (147–1599) ng/L, all: $P < 0.001$]. At univariate analysis, CS risk factors were age, EF, carbon dioxide, creatinine, norepinephrine, natriuretic peptides, whereas age and NT-proBNP level were the only multivariate predictors. On a 33-month follow-up, CS resulted among univariate predictors of cardiac death, NT-proBNP emerging as the only variable at multivariate analysis.
Conclusions: Daytime CS is frequent in CHF and is correlated with clinical severity, neurohormonal derangement, particularly of NT-proBNP, and long-term prognosis.
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Keywords: Cheyne–Stokes respiration; Natriuretic peptides; Norepinephrine; Heart failure; Prognosis

1. Introduction

Periodic breathing frequently occurs in patients with chronic heart failure (CHF), and is characterized by Cheyne–Stokes respiration (CS) either with central hypopneas or apneas alternating with hyperventilation [1]. CS has been more commonly detected at nighttime as sleep-related, in association with oxyhemoglobin desaturation, frequent arousals, sleep fragmentation [2], altered quality of life [3], and sympathetic overactivation [4–5], which may contribute to deterioration of cardiac function and reduced survival [6,7]. Few studies in small subsets have evaluated CS at daytime [4,8] in awake patients too, indicating a poor prognosis [9].

Neurohormonal derangement, involving activation of sympathetic, renin–angiotensin–aldosterone systems, and cardiac natriuretic peptide systems is a hallmark of CHF [10–11]. Plasma levels of brain natriuretic peptide (BNP)

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and of amino-terminal fragment of probrain natriuretic hormone (NT-proBNP), in particular, have been recognized as diagnostic and prognostic markers in CHF patients [12].

Whereas determinants of central sleep apneas have already been described [13], risk factors and clinical correlates of daytime CS remain unknown. Furthermore, the possible association of daytime CS and neurohormonal activation system has not been fully investigated. The aim of the present study was to evaluate prevalence and risk factors for daytime CS in CHF patients.

2. Methods

2.1. Patients

From September 2002 to November 2005, we selected 184 consecutive CHF patients with depressed left ventricular ejection fraction (EF, <45%) at echocardiography. Exclusion criteria were acute coronary syndrome within the preceding 6 months, severe chronic obstructive pulmonary disease, severe renal impairment (serum creatinine level >2.5 mg/dl), use of morphine, benzodiazepines, any psychotropic drug or theophilline derivatives. In order to focus on central hypopneas and apneas, additional exclusion criteria were also chosen, such as obesity (body mass index >30 kg/m^2) and history of snoring and upper airways obstruction. Of the 184 patients, 37 did not fulfill these criteria, leaving 147 patients for enrollment [(118 males and 29 females, mean age 64±12 years, body mass index 25±2.7 kg/m^2, EF 31± 8%, with ischaemic (46%), idiopathic (39%) or secondary (15%) cardiomyopathy (8% with hypertensive cardiomyopathy, and 7% with valvular disease), NYHA class I–II 65%, III–IV 35%)]. All patients were on optimal pharmacological treatment (82%: furosemide, 73%: carvedilol/bisoprolol, 84%: angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, 59%: spironolactone); 12 patients (9%) had previously received cardiac resynchronisation therapy.

The study was approved by the Institute's Ethical Committee and informed consent was obtained from all patients.

2.2. Cardiopulmonary exercise test, echocardiographic study and plasma assays

A symptom-limited cardiopulmonary test was performed on a bicycle ergometer using a ramp protocol with increments of 10 W/min (Vmax, Sensormedics, USA). All echocardiographic studies were performed by the same physician. Blood samples were drawn at 8 a.m. from an antecubital vein, after a 20-minute supine rest. Atrial natriuretic peptide (ANP), BNP, plasma catecholamines, plasma renin activity (PRA), aldosterone, and thyroid hormones were assayed as described elsewhere [10]; NT-proBNP was measured with an automated electrochemiluminescent immunoassay (Roche diagnostics, Germany).

2.3. Polygraphy

During the same morning, all subjects, in the supine position, were asked to relax without falling asleep, and during spontaneous breathing were evaluated for a 20-minute period, with a previously validated technique [4]. During each examination, we recorded a II electrocardiographic lead, chest and abdominal movement by electrical inductance, oronasal airflow, beat-to-beat blood pressure (Colin® tonometry, San Antonio, TX, USA), oxygen saturation (Pulse Oxymeter Pulsox-7, Minolta®) and end-tidal pCO2 signal (PETCO$_2$, Cosmoplus®, Novametrics). Data were digitized (300 sample/s), and stored on a personal computer. CS was defined either by the occurrence of cyclic episodes of apnea (cessation of flow and respiratory movements for ≥10 s) [5] or of hypopnea (reduction in the tidal volume greater than 50%, lasting ≥10 s, followed by a reduction in oxygen saturation of ≥4%), followed by hyperpnoea.

Fifty-three patients (36%) also underwent, within 24 h, a nocturnal continuous polysomnographic recording. An apnea–hypopnea index (defined as the number of apneas and hypopneas per hour) ≥20 was used as arbitrary cut-off to define relevant nighttime CS. Main clinical characteristics of patients receiving nocturnal recording were similar to those of the overall population: 41 males and 12 females, mean age 65±1 years, body mass index 25±0.3 kg/m^2, EF 31±1%, with ischaemic (44%), idiopathic (38%) or secondary (18%) cardiomyopathy, NYHA class I–II 63%, III–IV 37%.

2.4. Follow-up

Follow-up started at the time of hospital admission and continued until study termination. Independent interviewers obtained information directly from patients, relatives, or Institute cardiologists or general practitioners, regarding the date of death, between the time of discharge and September 2007. The primary end-point was cardiac death, including pump failure (defined as a death resulting from multiorgan failure caused by heart failure progression) and sudden death (defined as a witnessed cardiac arrest, death within 1 h after the onset of acute symptoms, or an unexpected death in a patient known to have been well within the previous 24 h). Information about time and cause of death was obtained from death certificates, post-mortem reports and family doctors. The individual follow-up ended with death or with cardiac surgery (ventricular assist device implantation, heart transplantation). No patient was lost to follow-up.

2.5. Statistical analysis

Statistical analysis was carried out using SPSS 12.0 (SPSS inc., Chicago, Il, USA). Due to the skewed distribution of BNP, NT-proBNP, norepinephrine, PRA and aldosterone, their natural logarithm was used for statistical
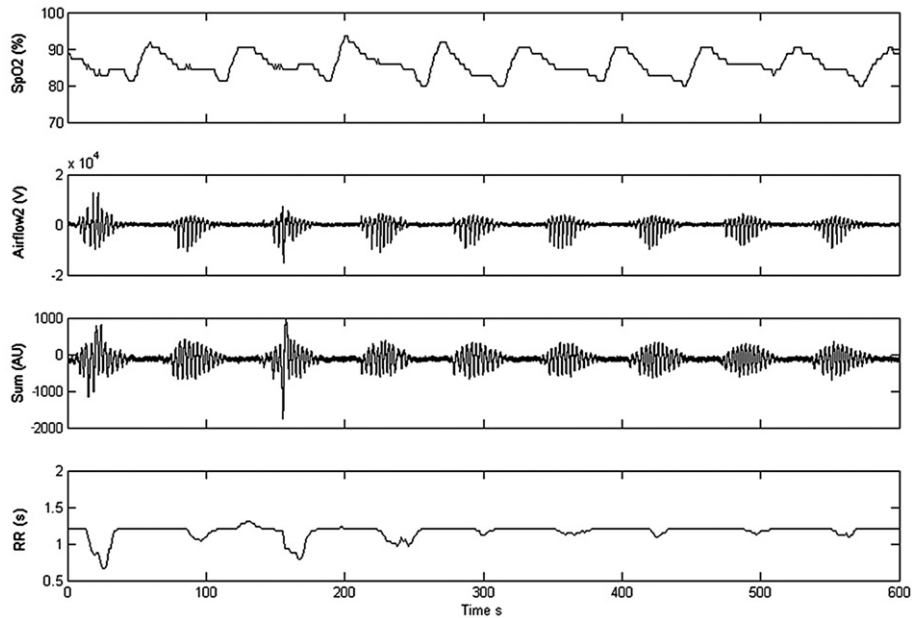
Fig. 1. Top-down: Time-course of oxygen saturation (SpO2), airflow, combined respiratory signal (Sum) from chest and abdominal inductance recordings, RR interval (RR) in a 62-year old patient with ischaemic cardiomyopathy and daytime Cheyne–Stokes respiration are shown.

analysis. The same principle was applied for other markers, when needed. Groups were compared for frequencies or categorical data (i.e., NYHA class) using the chi-squared test. Differences between groups in continuous variables were evaluated by the t-test for independent samples; differences between groups in categorical variables were evaluated by chi-square or Fischer exact test. Univariate and multiple logistic regression analyses were used to examine the association between several baseline clinical and neurohormonal variables and the presence of daytime CS occurrence. The candidate independent variables used for analysing risk factors for CS were selected on the basis of the strength of association with CS presence shown by previous studies in similar populations: body mass index, NYHA functional class, EF, presence of atrial fibrillation, presence of a paced cardiac rhythm, age, gender, mean resting $PETCO_2$ during wakefulness, medication, and cause of CHF, as previously described for sleep-related CS [13]. In addition, we have considered serum creatinine level, arterial pressure, left atrium area, maximum workload and peak oxygen consumption at cardiopulmonary test, plasma level of ANP, BNP, NT-proBNP, norepinephrine, renin activity, and aldosterone. Univariate predictors (age, ejection fraction, serum creatinine, NYHA functional class, peak oxygen consumption at cardiopulmonary test, plasma level of BNP, NT-proBNP and norepinephrine) were then considered for multivariate Cox proportional hazard regression analysis, with the exception of plasma BNP which, although closely related to NT-proBNP secretion, had a lower level of significance.

The predictive power of variables was quantified using receiver operating characteristic curves (ROC). A difference in the area under the curve (AUC) defined the increment in predictive power between different models. The statistical significance of differences in AUC from the line of "no information" and between different curves was evaluated with Mann–Whitney U-Statistics.

Survival curves were analysed using the Kaplan–Meier estimate and comparisons were made with log-rank test. In addition, Cox proportional hazards model was used to identify significant prognostic. The relative risk for each independent variable in the hazard equation was directly proportional to the risk brought by that variable to the model. All hazard ratios are presented with 95% confidence intervals and all P values are two-sided.

The candidate variables chosen for survival analysis have already been linked to long-term survival in previous studies conducted in similar populations: presence of daytime CS, NYHA functional class, EF, presence of atrial fibrillation, body mass index, age, gender, medication, serum creatinine level, peak oxygen consumption at cardiopulmonary test,
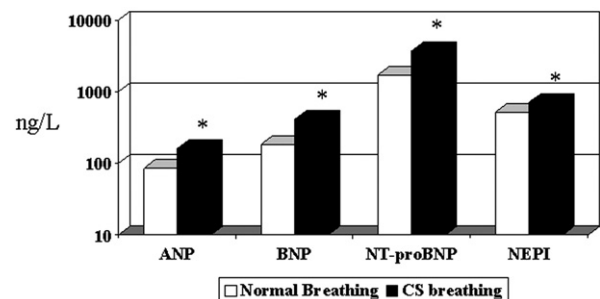

Fig. 2. Comparison of plasma concentration of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), amino-terminal fragment of probrain natriuretic peptide (NT-proBNP), and norepinephrine (NEPI) in patients with Cheyne–Stokes respiration (CS) and patients with normal breathing; *$P < 0.01$.

Table 1
General characteristics and neurohormonal findings in patients with normal breathing pattern and with Cheyne–Stokes breathing.

	Normal breathing	Cheyne–Stokes breathing	P value
Number	60	87	
Age (years)	60±14.5	66±10.2	0.01
Gender (F/M=n)	15/45	14/73	NS
ICM, n (%)	19 (32)	34 (39)	NS
BMI (kg/m^2)	24.6±2.9	25.1±2.6	NS
NYHA class	2.2±0.8	2.6±0.7	0.01
EF (%)	33±8.5	29±8.3	0.01
Creatinine (mg/dl)	1.08±0.3	1.25±0.4	0.01
Hb (g/dl)	13.2±1.2	12.8±1.5	NS
AF, n (%)	7 (13)	15 (18)	NS
Paced rhythm, n (%)	5 (9)	7 (8)	NS
ACEi/ARBs, n (%)	51 (85)	75 (86)	NS
Beta-blockers, n (%)	41 (74)	59 (71)	NS
Spironolactone, n (%)	31 (56)	51 (61)	NS
Digoxin, n (%)	23 (43)	28 (37)	NS
Diuretic, n (%)	44 (81)	65 (87)	NS
Workload (Watt)	87±33	71±29	0.04
peakVO$_2$ (mL/min/kg)	13.4±4	11.3±3.8	0.02
PETCO$_2$ (mm Hg)	37.9±3.8	33.1±4.2	0.001
ANP (ng/L)*	66.4 (18–103)	136.2 (57–230)	0.001
BNP (ng/L)*	64.1 (21–202)	284 (99–510)	0.001
NT-proBNP (ng/L)*	448.5 (147–1599)	2575 (814–3320)	0.001
PRA (ng/mL/h)*	1.65 (0.37–5)	1.78 (0.4–4.4)	NS
Aldosterone (ng/L)*	156 (109–242)	150 (88–191)	NS
Insulin (ng/L)	12±8.1	12±10.6	NS
Cortisol (ng/L)	168±74	164±62	NS
Epinephrine (ng/L)*	31 (10–42)	35 (19–52)	NS
Norepinephrine (ng/L)*	438 (331–681)	588 (395–939)	0.01
fT3 (ng/L)	2.4±0.1	2.3±0.1	NS
fT4 (ng/L)	12.5±0.4	13.7±0.5	NS
TSH (ng/L)*	1.5 (0.68–1.8)	1.5 (0.76–2.7)	NS

F: females; M: males; ICM: ischaemic cardiomyopathy; BMI: body mass index; NYHA: New York Heart Association; EF: left ventricular ejection fraction; AF: atrial fibrillation; ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin-receptor blockers; peakVO$_2$: peak oxygen consumption; PETCO$_2$: end-tidal carbon dioxide partial pressure; ANP: atrial natriuretic peptide; BNP: brain natriuretic peptide; NT-proBNP: N-terminal part of the pro-peptide of BNP; PRA: plasma renin activity; fT3: free triiodothyronine; fT4: free tetraiodothyronine; TSH: thyroid stimulating hormone; Hb: hemoglobin. Values are expressed as mean±SD for normally distributed variables, and (*) as median (25th–75th percentile) for non-normally distributed variables; % and (number of cases) are presented for binary variables.

ventilatory efficiency during exercise (expressed as slope of the ventilation vs VCO2 relation in its linear part), plasma level of BNP, NT-proBNP, norepinephrine, plasma renin activity. Among the univariate predictors (age, ejection fraction, atrial fibrillation, daytime CS, NYHA functional class, serum creatinine, plasma level of BNP and NT-proBNP), only the two with highest level of significance (EF and plasma level of NT-proBNP were then considered for multiple logistic regression analysis) due to the limited number of events during follow-up [14].

Values are presented as mean±standard deviation (SD), or median and interquartile range (for variables with non-

Table 2
Predictors at univariate and multivariate analysis of daytime CS respiration.

	Odds ratio	95% C.I.	P value
Univariate analysis			
PETCO$_2$	0.74	0.62–0.88	0.001
peakVO$_2$	0.87	0.76–0.99	0.030
EF	0.95	0.91–0.99	0.013
Workload	0.98	0.96–0.99	0.018
Age	1.05	1.02–1.08	0.002
BNP	1.78	1.36–2.32	0.000
NT-proBNP	1.87	1.41–2.48	0.000
ANP	2.07	1.36–3.16	0.001
NYHA	2.10	1.29–3.42	0.003
Norepinephrine	2.36	1.25–4.46	0.008
Creatinine	4.21	1.48–12.01	0.007
Multivariate analysis			
Age	1.06	1.01–1.13	0.034
NT-proBNP	1.93	1.13–3.30	0.017

CI: confidence intervals; PETCO$_2$: end-tidal carbon dioxide partial pressure; peakVO$_2$: peak oxygen consumption; EF: left ventricular ejection fraction; BNP: brain natriuretic peptide; NT-proBNP: N-terminal part of the pro-peptide of BNP; ANP: atrial natriuretic peptide; NYHA: New York Heart Association.

normal distribution) and P values<0.05 were considered significant.

3. Results

3.1. Prevalence of daytime breathing disorders

Daytime CS (Fig. 1) was found in 87 (59%) patients: central hypopneas were found in 47 (32%) and central apneas in 40 (27%) patients. All apneas and hypopneas were identified as having a central origin (characterized by simultaneous absence of both CO2 flow and chest/abdominal respiratory activity).

Table 3
Independent predictors at univariate and multivariate analysis of cardiac mortality.

	Hazard ratio	95% C.I.	P value
Univariate analysis			
peakVO$_2$	0.83	0.70–0.98	0.027
EF	0.89	0.83–0.95	0.001
Age	1.06	1.02–1.26	0.042
NYHA	2.29	1.29–4.07	0.005
CS	3.21	1.23–8.41	0.017
BNP	3.38	1.84–6.22	0.000
NT-proBNP	4.16	2.10–8.25	0.000
AF	4.69	1.70–12.91	0.003
Multivariate analysis			
NT-proBNP	2.98	1.35–6.56	0.007

PeakVO$_2$: peak oxygen consumption; EF: left ventricular ejection fraction; NYHA: New York Heart Association classification; CS: daytime Cheyne–Stokes respiration; BNP: brain natriuretic peptide; NT-proBNP: N-terminal part of the pro-peptide of BNP; AF: atrial fibrillation.

In the subset of patients who underwent nocturnal polysomnography, the presence of respiratory disorders at nighttime was accurately predicted by concomitant daytime CS (AUC 0.821, $P<0.01$ at receiver operating characteristic analysis, sensitivity 75%, specificity 75%). Patients with significant nocturnal CS (Respiratory Disorder Index >20) showed lower $PETCO_2$ (31.9 ± 5 vs 35.9 ± 5 mm Hg, $P=0.025$), higher BNP [540 (229–881) vs 159 (55–319) ng/L, $P=0.001$] and NT-proBNP level [3001 (1802–3547) vs 1238 (282–3352), $P<0.001$], and worse NYHA functional class (2.9 ± 0.5 vs 2.5 ± 0.5, $P=0.003$).

3.2. Clinical features, neurohormonal evaluation and breathing abnormalities

Presence of CS was significantly associated with a more severe clinical impairment (i.e. NYHA classification), age, reduced EF and functional capacity, lower levels of resting $PETCO_2$, and renal impairment. Patients with CS presented significantly higher plasma norepinephrine and cardiac natriuretic peptide levels (Fig. 2), as compared to patients with normal breathing, whereas no differences between the two groups were found for aldosterone, PRA, epinephrine and thyroid hormone plasma levels (Table 1).

3.3. Predictors of daytime respiratory disorders

At univariate analysis, the occurrence of daytime CS was predicted by age, low EF, low $PETCO_2$ level at rest, increased level of serum creatinine, plasma norepinephrine, ANP, BNP, and NT-proBNP (Table 2). However, at multivariate analysis age and plasma NT-proBNP level were the only independent predictors of CS; in particular, plasma NT-proBNP level resulted the best predictor (AUC 0.735, $P<0.001$, cut-off

value 634 pg/mL, specificity 61%, sensitivity of 85%, positive predictive value 76%, negative predictive value 73%).

3.4. Identification of risk factors for cardiac death

Median follow-up was 33 months (range 6–2000 days), during which 17 cardiac deaths occurred (3 sudden deaths and 14 due to congestive heart failure). Four non-cardiac deaths were excluded from the analysis.

At the univariate analysis, the following variables were predictive of cardiac death (Table 3): daytime CS (Fig. 3), increased plasma level of BNP and NT-proBNP (hazard ratios refer to a risk increase for one unit increment of their natural logarithm), age, presence of atrial fibrillation, higher NYHA class, EF. At the multivariate analysis, only NT-proBNP was an independent predictor of mortality.

4. Discussion

Our study indicates that central apneas and hypopneas occur in a high percentage of CHF patients at daytime, despite treatment with neurohormonal antagonists. Moreover, daytime CS is associated with adrenergic activation and overexpression of cardiac natriuretic hormones. Among all risk factors for daytime CS at univariate analysis, the concentration of plasma NT-proBNP was the best independent predictor of breathing abnormalities.

The prevalence of daytime CS in the present study is lower, as compared to earlier reports [4,8], likely due to improvement in pharmacological treatment during the last decade, in which beta-blockers had not been administered systematically [15]. The pathogenesis of CS in CHF is multifactorial and involves deregulation of negative feedbacks secondary to enhanced chemoceptive sensitivity [16–19], increased circulation time [18], increased filling pressures, and decreased functional residual capacity [20]. The combination of these factors elicits an excessive ventilatory response, lowering the difference between circulating levels of carbon dioxide and the apneic threshold, and thus favouring central apneas [21].

Daytime CS was significantly associated with more severe clinical impairment, reduced left ventricular EF and functional capacity, and lower levels of resting $PETCO_2$. The latter finding suggests a common pathogenesis for daytime and nocturnal CS. Indeed, the absence of obstructive apneas in awake patients at daytime confirms previous observations [4,8]: in awake status there is adequate stimulation of dilator muscles to maintain upper airway patency [22].

We also observed adrenergic activation in patients with daytime CS (likely associated with activated chemoreflex and CS-related oxyhemoglobin desaturation and hypoxia) [23], which in turn may contribute to ventricular arrhythmias and adverse prognosis [24,25], as well as increased expression of both atrial and B-type natriuretic peptides. Cardiac natriuretic hormone production is elicited by increased cardiac filling pressures [11], which have been
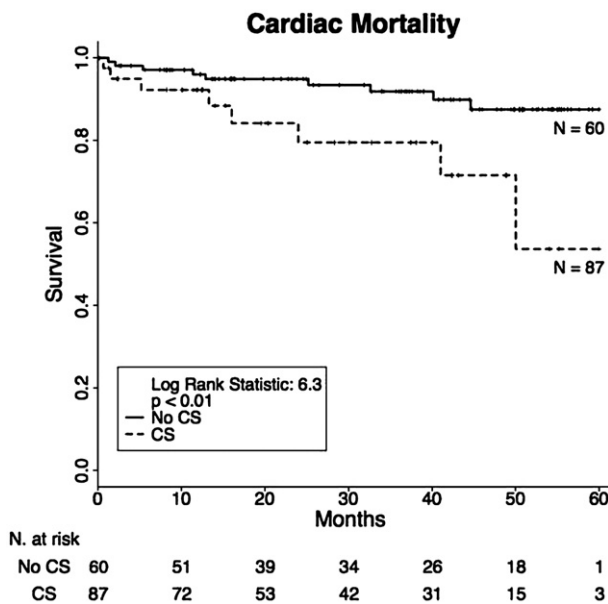

Fig. 3. Survival among 147 patients with chronic heart failure, according to the presence of daytime Cheyne–Stokes (CS) respiration.

associated with presence of sleep-related central apneas [26], sympathetic activation [11], and hypoxia [27].

Male gender, atrial fibrillation, age >60 years, and hypocapnia during wakefulness have been previously defined as risk factors for central sleep apneas by Sin, who, however, had not studied neurohormonal indices [13]. In our study, we found that, in addition to age and hypocapnia, left ventricular systolic dysfunction, NYHA class, functional capacity, and NT-proBNP were associated with CS. The ability of NT-proBNP level to predict daytime CS follows previous reports on increased BNP concentration in patients with sleep-related respiratory disorders [28,29], confirming the close relationship between cyclical respiratory pattern, haemodynamic overload and hypoxemic status [11,20].

Finally, our findings establish the value of resting daytime CS in the prediction of cardiac death in CHF, paralleling the observation by Corrà [30] on either sleep or exertional periodic breathing, and by La Rovere [31], though only plasma level of NT-proBNP resulted as independent prognosticator.

In a recent study by Brack et al., [32] CS during >10% of daytime was an independent predictor of death, after adjusting for BNP, age, and NYHA class. However, the authors enrolled only 60 patients and employed a long-term recording device without taking into account patient-to-patient variations in postural changes, speech and physical daily activity.

The limited sample size and the low cardiac event rate did not allow us to evaluate the association of daytime CS with specific causes of cardiac death. Furthermore, a thorough echocardiographic evaluation of left ventricular diastolic function was available only in a portion of study population, thus precluding its use in the overall analysis.

In conclusion, CS at daytime is easily and detectable in an objective way in CHF patients. It is a frequent manifestation and is associated with adrenergic activation and increased natriuretic hormone plasma level. Daytime recording of respiratory pattern, especially in the presence of increased NT-proBNP levels, could discriminate patients with breathing abnormalities. Further studies are necessary to evaluate specific therapies, targeting chemoceptive feed-back and adrenergic activation. Respiratory [33] and aerobic physical training [34], in particular, may have the potential to improve life quality and life expectancy in this particular subset of CHF patients.

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