Implications of Cheyne-Stokes Breathing in Advanced Systolic Heart Failure

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ABSTRACT

Background: Cheyne-Stokes breathing (CSB) has been associated with heart failure (HF) patients for many years; however, its true prevalence and its prognostic implications are still obscure.

Hypothesis: The goal of this study was to investigate the prevalence and the possible prognostic implications of nocturnal CSB in advanced heart failure patients.

Methods: We performed single night full polysomnography ambulatory sleep studies in 71 HF patients. We analyzed the patients' sleep studies, clinical and laboratory data, and 6 month mortality.

Results: A total of 71 chronic systolic HF patients were analyzed, 60 males, 11 females, age 65 ± 13 years. Mean left ventricular ejection fraction was $27\% \pm 11\%$. Short episodes of CSB (at least 3 min duration) were present in all patients, and mean CSB duration was 1 hour. CSB duration was associated significantly with both high serum levels of N-terminal prohormone brain natriuretic peptide (NT-proBNP) as well as with 6 month mortality. Log CSB time had a significant correlation with log NT-proBNP ($r = 0.5$, $P < .0001$). Based on median CSB duration, the Kaplan-Meier survival curve analysis showed significant association with 6 month mortality ($P = .03$).

Conclusions: CSB prevalence in advanced HF patients is higher than previously reported and is associated with increased serum levels of NT-proBNP and higher 6 month mortality.

Introduction

Cheyne-Stokes breathing (CSB) has been associated with heart failure for more than 2 centuries and yet its incidence and clinical implications are still being debated. Therefore, we conducted ambulatory sleep studies in 71 advanced systolic heart failure (HF) patients in order to assess the prevalence and consequences of CSB. To evaluate the possible prognostic implications of CSB in HF, we analyzed sleep study results, clinical data, laboratory parameters, and followed patient mortality for 6 months.

Patients and Methods

We screened 74 consecutive patients for our study. All these patients were followed in our HF center for symptomatic HF for at least 3 months duration and were treated according to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines. All patients were clinically considered to be of relatively stable HF status without acute decompensation. None of the patients had had a previous significant neurological event or had been screened before for sleep apnea. One patient refused to participate in the study and 2 patients who slept less than 4 hours were excluded as only sleep studies with at least a total of 4 hours of sleep were analyzed. Accordingly, the number of patients included in the final analysis was 71 (60

males, 11 females, age 65 ± 13 years). Patient characteristics are detailed in Table 1. Each patient underwent a single full night of sleep at home with monitored polysomnography and Holter monitoring using Somte ambulatory and Mortara H12 scribe Holter respectively. WideMed's Morpheus, an FDA approved system, was used for scoring with computerized and standard manual analysis. We defined apnea, hypopnea, and CSB according to American Academy of Sleep Medicine Task Force guidelines.^{1,2}

A blood sample for N-terminal prohormone brain natriuretic peptide (NT-proBNP) was drawn on the same night of the sleep study. Serum NT-proBNP was measured with the Elecsys proBNP electro-chemiluminescence immunoassay run on the Elecsys 1010 (Roche Diagnostics, Indianapolis, IN).

Statistical analysis was performed using SPSS 13.0. A P value $< .05$ was considered to represent statistical significance.

The study was approved by the Helsinki committee of the Lady Davis Carmel Medical Center, Haifa, Israel. All patients signed an informed consent prior to inclusion in the study.

Results

Sleep analysis: Mean total sleeping time was 5 ± 1 hours. Rapid eye movement sleeping time was $17\% \pm 8\%$ of total

Table 1. Patient Characteristics (n = 71)

Age (years)	64±13
Male/Female	60/11
Body mass index (kg/m ²)	29±6
Mean New York Heart Association (NYHA) class	2.8
NYHA class 3–4, n (%)	40 (56)
Left ventricular ejection fraction (%)	27±11
End-diastolic diameter (mm)	61±7
Chronic renal failure, (Cr > 2 mg%) n (%)	9 (13)
Ischemic cardiomyopathy, n (%)	43 (61)
Systolic blood pressure, mm Hg	118±21
Atrial fibrillation, n (%)	22 (31)
QRS width (msec)	133±47
Diabetes mellitus, n (%)	30 (42)
β-Blocker, n (%)	68 (96)
Angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker, n (%)	61 (86)
Serum creatinine (mg%)	1.4±0.7
Hemoglobin (g/dl)	13±2
Log NT-proBNP (pg/ml)	3.2±0.6
6 months mortality, n (%)	7 (10)

sleeping time. Deep sleep time was 9%±8% of total sleeping time. Mean awakening and arousals were 46±22 per hour. Mean apnea-hypopnea index (AHI) was 35±17 episodes per hour; 15±12 were obstructive. In 39 (55%) patients there was AHI of more than 30 per hour, 32 (45%) patients had AHI of 5–30 per hour.

CSB analysis: The sleep analysis showed that all patients experienced short episodes of CSB (duration of at least 3 min), and 66 (94%) of the patients had CSB of more than 10 minutes. Mean CSB time duration was 83±69 minutes with a median of 60 minutes.

CSB time ratio, defined as total time of CSB divided by total sleeping time, was 31±30. All CSB episodes were associated with desaturation, defined as ≥2% decrease in desaturation via pulse oxymetry. CSB was associated with both decreased deep slow wave sleeping time and increased prevalence of premature ventricular beats ($r = -0.3$, $P = .02$, $r = 0.3$, $P < .01$, respectively).

We analyzed the CSB time correlation with prognostic parameters: serum NT-proBNP level and 6 month mortality follow-up. In a stepwise linear regression model for log

Table 2. Significant Predictors for Log NT-proBNP

Parameter	Significance	Partial Coefficient
Log CSB time	<.0001	0.5
Creatinine	.001	0.3
Body mass index	.02	−0.03
QRS width	.04	0.003

NT-proBNP we included the following parameters: age, gender, body mass index, QRS width, New York Heart Association (NYHA) class, left ventricular ejection fraction, ischemic etiology, creatinine, AHI, and log CSB time. Of these parameters only 4 were found to be significant for log NT-proBNP: creatinine, body mass index, QRS width, and log CSB time, which was the most significant (Table 2).

From the sleep study performance, we followed patients for 6 month mortality. A total of 7 (10%) patients died within 6 months. Death mean time duration was 3.5±1.9 months. The etiology of death was heart failure in 5 patients and cardiac arrhythmia in 2 patients.

We used a t test and a χ^2 to compare the characteristics of patients who died and the patients who survived, (Table 3). The significant different parameters between the 2 groups were age, body mass index, usage of a β-blocker and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and log CSB time. We used a logistic regression model to test for mortality including the following parameters: age, gender, body mass index, QRS width, NYHA class, left ventricular ejection fraction, ischemic etiology, creatinine, log NT-proBNP, AHI, and log CSB time. The only parameter which was found to be significant for mortality was log CSB time ($P = .02$). The cumulative survival rates for patient with CSB time below the median of 60 minutes were significantly higher ($P = .03$) compared to patients with higher CSB time (Figure 1).

Discussion

In this study, we analyzed ambulatory sleep studies of 71 severe chronic systolic HF patients, focusing on CSB pattern. The 2 main conclusions of our study are that in advanced HF patients, episodes of CSB are much more prevalent than previously reported, and are associated with poor prognosis as manifested by both high 6 month mortality and higher serum NT-proBNP levels.

At least short episodes of CSB occurred in all the study patients. Previous reports of HF estimated a CSB prevalence of 30%–50%, a significantly lower range than in our study.^{3,4} Since sleep disorder prevalence is correlated to HF severity,⁵ it is conceivable that our findings represent the true prevalence in such a cohort of patients with advanced disease. In most of the previous studies,⁶ sleep apneas in HF patients were assessed by using polysomnography

Table 3. Clinical Parameters in Relation to 6 Months Survival

	Patients Alive (64)	Patients Dead (7)	P Value
Age (years)	64±14	75±7	.03 ^a
Male/Female	54/10	6/1	.2
Body mass index (kg/m ²)	30±6	26±2	.01 ^a
New York Heart Association (NYHA)	34 (53)	6 (86)	0.2
Class 3–4, n (%)			
QRS width (msec)	133±47	138±42	.7
Left ventricular ejection fraction (%)	28±11	23±7	.3
End-diastolic diameter (mm)	61±8	61±6	.9
Ischemic cardiomyopathy, n (%)	36 (56)	7 (100)	.06
Chronic renal failure; (Creatinine >2 mg%), n (%)	8 (13)	1 (14)	.6
Atrial fibrillation, n (%)	18 (28)	4 (57)	.2
β-Blocker, n (%)	63 (95)	5 (71)	.01 ^a
Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers, n (%)	58 (91)	3 (43)	<.01 ^a
Log CSB time	1.7±0.4	2.1±0.3	.02
Serum creatinine (mg%)	1.3±0.7	1.6±0.4	.3
Hemoglobin (g/dl)	12.6±1.7	12.5±2	.8
Log NT-proBNP (pg/ml)	3.1±0.6	3.5±0.5	.1

^a*P* < .05.

Figure 1. Survival curves according to CSB time below and above median time (60 min).

in an ambulatory hospital setting and/or sleep laboratory facilities. As reported by others, some sick HF patients refused to participate in sleep studies due to the need to

either travel or to stay in the hospital/sleep laboratory.³ This may in fact have resulted in a referral bias. Since we used a simple and reliable ambulatory mode of monitoring,⁷ we believe that our data represent the true magnitude of CSB in severe chronic symptomatic systolic HF patients.

Although CSB has been known for many years to be associated with HF,^{8,9} its mechanism, prognostic implications, and possible therapies are still controversial.^{10–13} Although in this current study we concentrated solely on a specific pattern of central sleep disturbance, namely CSB, other forms of sleep apnea have been identified in HF patients, including obstructive and central apneas.^{6,12,14}

A few studies of HF patients suggested that high AHI, obstructive, and central apneas are all associated with mortality.^{9,15–17} Of note, we found no impact of AHI on mortality in our patients. We demonstrated that CSB duration is significantly associated with a high NT-proBNP serum level, a well-known prognostic marker in the HF patient.^{18,19}

The most prevalent theory regarding CSB pathogenesis claims that elevated left ventricular filling pressures

result in pulmonary congestion and J receptors activation, ultimately stimulating hyperventilation and hypocapnia. This hyperventilation initiates the cycle of CSB as the CO₂ level falls below the threshold for ventilation, followed by apnea until CO₂ rises above the threshold again and stimulates ventilation.²⁰ Our finding that CSB is significantly associated with NT-proBNP, a direct marker of pressure overload, supports the concept that pressure overload is an important part of CSB.²¹ There are several possible mechanisms for the association between CSB events and mortality, which was demonstrated in the current study. It has been shown before that CSB is associated with oscillations in both heart rate and blood pressure.^{22,23}

We showed in our study that high CSB time was mildly but significantly associated with both an increased prevalence of premature ventricular beats and a decrease in deep slow wave sleeping time. The latter is conceived as a time period of decreased sympathetic activity and its relative decrease in patients with CSB creates an imbalance of high sympathetic tone.²⁴ This thesis is supported by other observations, in which the “smoking gun” of CSB in HF is repeated episodes of hypoxemia with a contribution of ventricular arrhythmia and high sympathetic tone.^{5,25,26} Moreover, several studies demonstrated that even short daytime oscillatory breathing patterns are associated with poor outcome.^{27,28}

The main, as yet unsolved, question is whether CSB is merely a reflection of HF disease severity or whether it actually causes the clinical course of the HF disease to deteriorate.²⁰ We believe that our current results support the notion that CSB is an important signal in HF and suggest that CSB is a cause rather than a reflection of HF severity.²¹

Although we cannot claim that CSB is a direct cause of mortality in HF patients, it is conceivable that repeated episodes of CSB may deteriorate HF disease over time.^{5,25} Several study limitations should be noted. We recognize that our study is relatively small, based on a single night recording and we fully agree with others that further studies in this arena are needed.²⁹ As per our original study goals, we concentrated specifically on CSB and its clinical implications in advanced systolic HF patients. Accordingly, we did not analyze possible clinical implications of other forms of sleep apnea, such as obstructive apnea, nor did we conduct a treatment phase such as employing an auto-titrating servo ventilator for CSB, as these issues were beyond the scope of our study.

Conclusions

Our study demonstrated that advanced chronic systolic HF patients have a higher prevalence of CSB than previously reported. CSB is associated with both high 6 month mortality and elevated serum NT-proBNP levels. Accordingly, CSB in HF patients should be regarded as a marker of disease severity rather than just a respiratory pattern of breathing.

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