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Prognostic Value of Nocturnal Cheyne-Stokes Respiration in Chronic Heart Failure

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Background—Nocturnal Cheyne-Stokes respiration (CSR) occurs frequently in patients with chronic heart failure (CHF), and it may be associated with sympathetic activation. The aim of the present study was to evaluate whether CSR could affect prognosis in patients with CHF.

Methods and Results—Sixty-two CHF patients with left ventricular ejection fraction $\leq 35\%$, in NYHA class II to III, underwent clinical evaluation, Doppler echocardiography, ergospirometry, phenylephrine test, Holter recording, and a sleep study to evaluate the occurrence of CSR, expressed as percentage of periodic breathing, and apnea/hypopnea index (AHI) (ie, the number of apneas and hypopneas per hour of recording). During a mean follow-up of 28 ± 13 months, 15 patients died of cardiac causes. Nonsurvivors were in a higher NYHA functional class than survivors ($P < 0.001$) and had a more depressed left ventricular ejection fraction ($P < 0.03$), a shorter deceleration time of early filling ($P < 0.05$), larger left and right atria ($P < 0.05$ and $P < 0.02$, respectively) and a lower peak $\dot{V}O_2$ ($P < 0.05$). Nonsurvivors also spent a greater percentage of the night in periodic breathing ($P < 0.01$) with a greater AHI ($P < 0.03$) and showed lower values of diurnal baroreflex sensitivity ($P < 0.05$) and of heart rate variability (sdNN: $P < 0.01$). Multivariate analysis revealed the AHI (χ^2 , 10.4; $P < 0.01$), followed by left atrial area (χ^2 , 5.7; $P < 0.01$), as the only independent and additional predictors of subsequent cardiac death. Patients at very high risk for fatal outcome could be identified by an AHI $\geq 30/h$ and left atria ≥ 25 cm².

Conclusions—The AHI is a powerful independent predictor of poor prognosis in clinically stable patients with CHF. The presence of an AHI $\geq 30/h$ adds prognostic information compared with other clinical, echocardiographic, and autonomic data and identifies patients at very high risk for subsequent cardiac death. (*Circulation*. 1999;99:1435-1440.)

Key Words: heart failure ■ sleep ■ prognosis

Cheyne-Stokes respiration (CSR) is a form of disordered breathing characterized by recurrent episodes of central apneas or hypopneas, alternating with hyperpneas, during which there is a crescendo-decrescendo pattern of tidal volume.^{1,2}

Since its first description, this breathing disorder has been commonly observed both in awake conditions and during sleep, not only in acute heart failure but also in many clinically stable patients with chronic heart failure (CHF) and left ventricular systolic dysfunction.³⁻⁷ Although several experimental and clinical studies have described its potential detrimental effects on autonomic and cardiac function,^{3,8} sleep disordered breathing has been given modest attention in the heart failure literature, and it has not been systematically evaluated in any of the large studies that have examined the natural history of heart failure.⁹ Mortality appears to be increased in heart failure patients with nocturnal CSR compared with those without CSR, despite a similar degree of left ventricular dysfunction.^{6,7,10} However, contrasting results

have been reported concerning the prognostic value of nocturnal CSR.^{6,7,10,11}

Accordingly, the aim of the present study was to evaluate the impact of nocturnal CSR on survival in a population of patients with CHF.

Methods

Consecutive patients with CHF due to either ischemic or idiopathic dilated cardiomyopathy were enrolled from the Heart Failure Unit of the Cardiology Department of our institution. The entry criteria were (1) at least 1 previous episode of clinical heart failure, (2) an echocardiographic left ventricular ejection fraction $\leq 35\%$, and (3) stable clinical conditions under oral therapy for at least 1 month before evaluation. Patients were ineligible if they had a body mass index > 30 kg/m² or if they had any of the following: atrial fibrillation, primary valvular heart disease, coronary artery bypass procedures during the previous 6 months, obstructive lung disease as demonstrated by a forced expiratory volume in 1 second/forced vital capacity $< 70\%$, clinical signs of central or peripheral nervous system impairment or a history of stroke, or cocaine or alcohol abuse. Sixty-six patients (8 women) 57 ± 9 years old met the entry criteria and were enrolled in the study. All patients gave written

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informed consent to perform the study protocol and to participate in this prospective study, which had been approved by the Science and Ethics Committee of our institution.

Study Protocol

The study consisted of 2 parts: (1) functional evaluation at entry and (2) follow-up. Entry evaluation included historic data collection, functional classification, Doppler echocardiography, ergospirometry, 24-hour Holter recording, the phenylephrine test, and a sleep study. The functional status of patients was determined according to the classification of the New York Heart Association (NYHA).

Echocardiography

A complete 2-dimensional echocardiography and a Doppler ultrasound examination were performed by standard techniques with a Hewlett-Packard ultrasound system (model 77729-A or 77622-A). Left ventricular volumes were calculated from orthogonal apical views by the area-length method. The ejection fraction was derived from the standard equation. The maximal atrial area and the right ventricular end-diastolic diameter 1 cm below the tricuspid annulus were also measured. For the mitral Doppler variables, traces of 5 to 8 consecutive cardiac cycles were analyzed with a microcomputer-based digitizing system, and deceleration time of early filling was measured. Mitral and tricuspid regurgitation were semiquantitatively graded by color flow Doppler as none, mild, moderate, or severe as previously reported.¹²

Ergospirometry

Multistage symptom-limited bicycle exercise testing with spirometry was used to evaluate the peak oxygen consumption.

Baroreflex Sensitivity Assessment

Arterial baroreceptor function was evaluated by administration of phenylephrine (2 to 4 $\mu\text{g}/\text{kg}$), as previously described.¹³ Baroreflex sensitivity (BRS) was measured in ms/mm Hg as the slope of the regression line relating the RR interval to systolic arterial pressure increments.

24-Hour Ambulatory ECG Recording

Recordings were performed by means of a commercial device (Marquette 8500), and measures of RR-interval variability were derived. Heart rate variability was assessed both over the whole 24-hour period of the recording and separately during the night (from 12 PM to 5 AM) and day (from 7 AM to 7 PM) periods. The mean normal-to-normal (NN) intervals, the standard deviation of NN (sdNN), and the percentage of >50-ms differences between adjacent NNs (pNN50) were evaluated.¹⁴

Sleep Study

All patients underwent an overnight sleep study by means of an unattended system (Night-Watch, Healthdyne Inc) recording body position, eye and leg movements, cardi tachography, nasobuccal air flow, chest and abdominal effort, and pulse oximetry. A central apnea was defined as the absence of flow and thoracoabdominal movements lasting at least 10 seconds. Central hypopnea was defined as a $\geq 50\%$ decrease in the sum of thoracoabdominal movements lasting 10 seconds or more, followed by a reduction in SaO_2 of $\geq 2\%$. Periodic breathing was measured and reported as a percentage of total recording time and as a central apnea-hypopnea index (AHI), which was defined as the number of apneas and hypopneas per hour of recording. When obstructive events exceeded 5 episodes per hour, the patient was excluded from further analysis.

Follow-Up

After entry evaluation, patients were seen in our outpatient clinic at regular intervals of 6 months. The follow-up of patients who did not attend the scheduled appointments was obtained by personal communication with the patient's physician or by means of a telephone interview with the patient. The outcome event considered was cardiac mortality.

Statistical Analysis

All descriptive data are given as mean \pm SD. Differences between patients were compared by Student's unpaired *t* test and frequency of parameters and events by χ^2 test with Yates' correction. In the comparison between survivors and nonsurvivors, patients who received heart transplants and those with noncardiac death were excluded from analysis. Those variables that showed a significant association with the outcome ($P < 0.1$) were included in a multivariate logistic stepwise regression analysis model. Survival was estimated by the product-limit Kaplan-Meier method, in which heart transplantations and noncardiac deaths were included as censored data. Differences between survival curves were tested with the log-rank χ^2 statistic. A value of $P < 0.05$ was considered significant.

Results

Of the 66 patients initially enrolled, 4 were excluded because they presented periodic breathing with obstructive apneas, leaving 62 patients as the final study population. The cause of heart failure was ischemic dilated cardiomyopathy in 33 patients and nonischemic dilated cardiomyopathy in 29. Patients were taking a variety of medications, including digitalis (78%), ACE inhibitors (94%), nitrates (48%), and diuretics (91%). Mean ejection fraction was $23 \pm 6\%$. At the sleep study, 46 patients (74%) showed an AHI $\geq 10/\text{h}$ during the night.

Follow-Up

Patients were followed up for 28 ± 13 months. During that period, 21 patients had at least 1 new episode of CHF that required hospitalization, 6 patients received heart transplants, 2 patients died of noncardiac causes, and 15 patients died of cardiac causes: sudden death (7 patients), refractory heart failure (7 patients), and myocardial infarction (1 patient). The 1- and 2-year cumulative mortality rates were 12% and 25%, respectively. Clinical, echocardiographic, sleep, and autonomic data are summarized in Table 1. Nonsurvivors were in a higher NYHA functional class than survivors ($P < 0.001$). They had a more depressed left ventricular ejection fraction ($P < 0.03$), a shorter deceleration time of early filling ($P < 0.05$), larger left and right atria ($P < 0.05$ and $P < 0.02$, respectively), a larger right ventricular diameter ($P < 0.03$), and a lower peak $\dot{V}\text{O}_2$ at the cardiopulmonary test ($P < 0.05$). Nonsurvivors also had a greater percentage of the night in periodic breathing ($P < 0.01$) with a higher value of AHI ($P < 0.03$), but no difference was found in the time spent at $< 90\%$ and $< 85\%$ SaO_2 levels. Finally, nonsurvivors showed a more depressed diurnal BRS ($P < 0.05$) and lower 24-hour and nocturnal mean NN ($P < 0.01$), sdNN ($P < 0.01$ and $P < 0.05$, respectively), and pNN50 ($P < 0.01$). No specific medications at baseline emerged as significantly associated with prognosis.

Multivariate regression analysis revealed AHI (but not percent of periodic breathing) followed by left atrial (LA) area as the only independent and additional predictors of subsequent cardiac death (Table 2). Mortality was significantly higher in patients with AHI $\geq 30/\text{h}$ than in those with AHI $< 30/\text{h}$ (59% versus 14%, $P < 0.001$) and in patients with LA area $\geq 25 \text{ cm}^2$ than in those with LA area $< 25 \text{ cm}^2$ (43% versus 12%, $P < 0.01$) and considerably higher in patients with both higher AHI and enlarged LA area than in those without (75% versus 5%, $P < 0.001$). Survival according to

TABLE 1. Baseline Characteristics According to Mortality

	All Patients (n=54)	Survivors (n=39)	Nonsurvivors (n=15)
Age, y	57±9	58±9	56±10
NYHA Class III	8 (15)	2 (5)	6 (40)†
Peak $\dot{V}O_2$, mL · kg ⁻¹ · min ⁻¹	15.9±4.6	16.7±4.5	12.8±3.4*
Medications			
Digoxin	41 (76)	27 (69)	14 (93)
ACE inhibitors	46 (85)	34 (87)	12 (80)
Diuretics	48 (89)	34 (87)	14 (93)
Nitrates	28 (52)	17 (31)	11 (73)
Amiodarone	11 (20)	6 (15)	5 (33)
Echocardiographic data			
LVEF, %	23±6	24±7	21±4*
LVEDVI, mL/m ²	131±43	127±47	145±29
LVESVI, mL/m ²	101±39	96±42	112±26
Early Dec time, ms	150±48	159±51	127±30*
LA area, cm ²	25±7	23±8	28±6*
RA area, cm ²	17±6	16±5	20±6*
RVEDD, mm	39±8	38±7	43±7*
MR moderate-severe	36 (67)	23 (59)	13 (87)
TR moderate-severe	12 (22)	7 (31)	5 (33)
Sleep data			
AHI, n/h	25±20	20±15	38±23†
PB, %	36±29	29±27	56±24†
SaO ₂ <90, %	8.7±13.5	7.0±13.7	10.3±13.3
Autonomic data			
BRS, ms/mm Hg	4.3±4.7	5±5	2.5±3.4*
Mean NN, ms	780±720	803±127	719±72†
sdNN, ms	103±46	114±47	78±28†
pNN50, %	5.1±9.2	6.7±10.4	0.8±1.1†
Nocturnal mean NN, ms	874±172	912±180	772±93†
Nocturnal sdNN, ms	71±35	79±35	50±25*
Nocturnal pNN50, %	6.1±10.4	8.2±11.6	0.8±1.5†

LVEF indicates left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; Early dec time, deceleration time of early filling; RA, right atrium; RVEDD, right ventricular end-diastolic diameter; MR, mitral regurgitation; TR, tricuspid regurgitation; PB, periodic breathing; and BRS, baroreflex sensitivity. Data are mean±SD or number (%) of patients.

*P<0.05; †P<0.01.

the value of AHI and LA area is shown in Figure 1. The cumulative 1- and 2-year cardiac mortalities were, respectively, 21.4% and 50% in patients with AHI ≥30/h versus 5.4% and 26.2% in those with AHI <30/h (P<0.01); 16% and 62.5% in patients with LA ≥25 cm² versus 3.8% and 6.6% in those with LA <25 cm² (P<0.01); and 33.3% and

TABLE 2. Independent Predictors of Cardiac Mortality by Multivariate Logistic Stepwise Regression Analysis

Variable	β	P	Model χ ²	P
AHI, n/h	0.06	0.005	10.4	0.0013
LA area, cm ²	0.11	0.027	16.1	0.0003

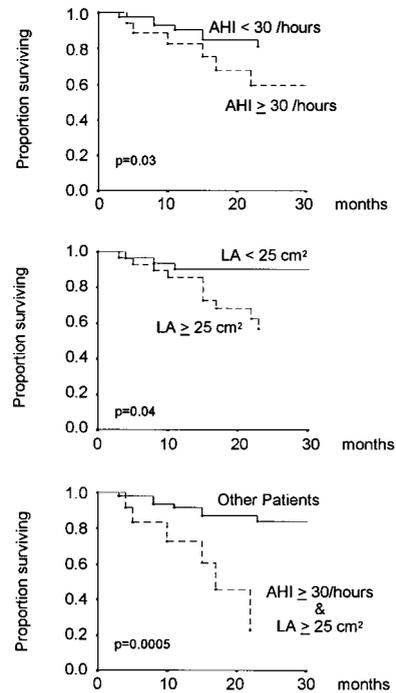


Figure 1. Cumulative survival without cardiac mortality according to AHI, LA area, and their combination.

85.8% in patients with both AHI ≥30/h and LA ≥25 cm² versus 4.8% and 20.8% in the other patients (P<0.0001). The risk of cardiac death increased progressively with an increase in the value of AHI and LA dimensions: patients at very high risk for fatal outcome can be identified by an AHI ≥30/h and enlarged left atria ≥25 cm² (Table 3 and Figure 2).

Baseline Characteristics of Patients With Breathing Disorders

Patients with AHI ≥30/h, compared with those with AHI <30/h, showed a more impaired ejection fraction (P<0.05), a shorter deceleration time of early filling (P<0.01), a lower peak $\dot{V}O_2$ (P=0.02), and a lower level of diurnal Po₂ (P=0.02) but the same level of Pco₂ (Table 4). However, AHI was poorly related to ejection fraction (r=-0.22, P=NS), deceleration time of early filling (r=-0.28, P<0.05), and peak $\dot{V}O_2$ (P=-0.26, P=NS). Patients with AHI >30/h showed a depressed BRS and an impaired heart rate variability as expressed by sdNN and pNN50 in both the 24-hour (sdNN, P<0.001; pNN50, P<0.01) and night periods (nocturnal sdNN, P<0.01; nocturnal pNN50, P<0.01). The value of AHI was well correlated with sdNN (r=-64, P<0.0001) and BRS (r=-40, P<0.01).

TABLE 3. Mortality Odds According to AHI and LA Area

AHI, n/h	LA Area 15 cm ²	LA Area 25 cm ²	Area 30 cm ²
10	0.17	0.43	0.68
20	0.31	0.77	1.22
30	0.55	1.38	2.19
35	0.74	1.86	2.94
40	0.99	2.49	3.94

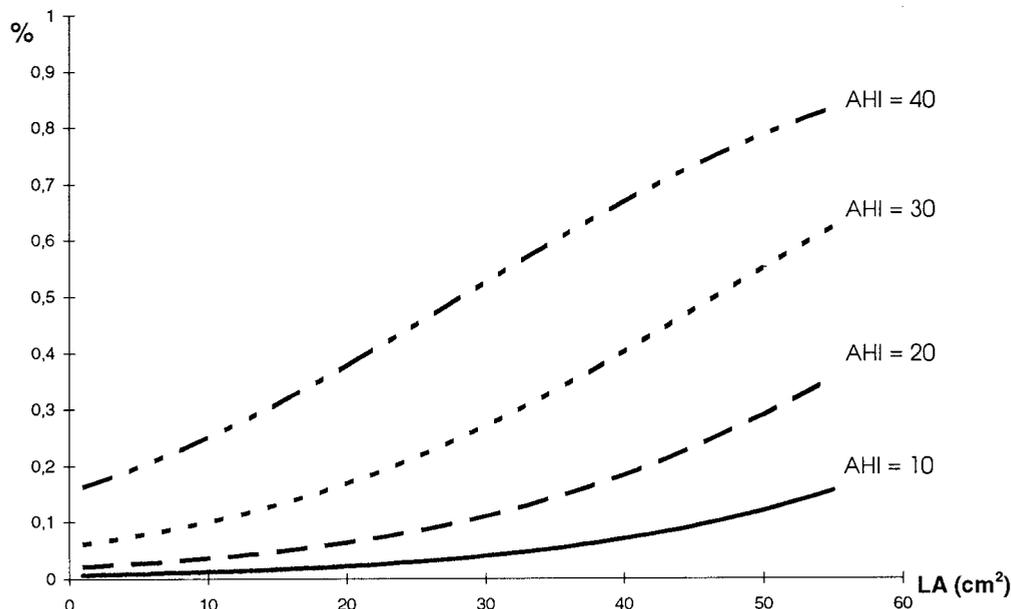


Figure 2. Mortality occurrence according to AHI and LA area.

Multivariate logistic analysis, including in the model ejection fraction, NYHA class, deceleration time of early filling, and BRS, indicated BRS to be the only predictor of the sleep-related breathing disorder (χ^2 , 15.5; $P < 0.001$).

Discussion

The present study shows that nocturnal CSR has a negative effect on survival in patients with moderate to severe CHF due to ischemic or nonischemic dilated cardiomyopathy.

TABLE 4. Baseline Characteristics According to AHI

	AHI <30/h (n=44)	AHI ≥30/h (n=18)
NYHA Class III, n (%)	3 (7)	8 (44)†
LVEF, %	24±6	20±5*
Early dec time, ms	158±51	126±25†
RA area, cm ²	16±4	20±7*
LA area, cm ²	24±8	27±7
RVEDD, mm	37±6	43±9*
LVESVI, mL/m ²	98±42	120±43
LVEDVI, mL/m ²	128±47	152±46
Peak $\dot{V}O_2$, mL · kg ⁻¹ · min ⁻¹	17±4	13±4*
Po ₂ , mm Hg	79±9	72±11†
PcO ₂ , mm Hg	37±3	37±3
BRS, ms/mm Hg	5.1±4.7	1.3±2.7†
Mean NN, ms	793±127	738±80
sdNN, ms	119±44	67±18‡
pNN50, %	7.2±10.8	1.03±1.4†
Nocturnal mean NN, ms	920±189	789±93†
Nocturnal sdNN, ms	81±36	53±23†
Nocturnal pNN50, %	9.1±12	0.7±1.2†

Abbreviations as in Table 1. Data are mean±SD or number (%) of patients. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.0001$.

Although many variables are associated with cardiac mortality, our data indicate that this nocturnal breathing disorder gives independent and additional prognostic information in clinically stable patients, particularly in those with a more enlarged LA.

Previous studies on the prognostic value of nocturnal CSR in patients with heart failure are limited and contradictory. Initially, the prognostic value of nocturnal periodic breathing was reported as a corollary result of studies on CHF patients.^{6,7} The first study that specifically aimed to test survival in patients with stable CHF was conducted by Hanly and Zuberi-Khokhar,¹⁰ who reported a 3-year mortality of 56% in 8 patients with nocturnal CSR compared with 11% in 8 patients without CSR, despite similar functional status and left ventricular ejection fraction. By contrast, Andreas et al¹¹ did not find any difference in mortality at 1, 2, and 4 years in 36 patients with or without CSR as defined by >20% CSR of total sleep time. This discrepancy may be due to either the different characteristics of the patients, the time of the evaluation, or the definition of breathing disorder used in the analysis. Specifically, in the study by Andreas et al, patients were evaluated when they had no signs of clinical acute heart failure. However, the duration of clinical stability was unclear.

Furthermore, in the Andreas study, nocturnal breathing disorder was evaluated as a percentage of periodic breathing, and the number of events, ie, apneas and hypopneas, was not considered.

In the present study, AHI, but not percentage of periodic breathing, emerged as the most powerful independent predictor of cardiac mortality among demographic, clinical, echocardiographic, and some autonomic and sleep data, indicating the greater impact on survival of the number of respiratory events rather than the total time spent in periodic breathing. LA area was shown to be an additional and independent prognostic indicator, in line with some data reported in the

literature.¹⁵ The risk of cardiac death increased progressively with the value of AHI as well as with LA area: patients at very high risk for fatal outcome can be identified by an AHI $\geq 30/h$ and enlarged LA ≥ 25 cm². Nevertheless, in patients with isolated enlarged LA without important breathing disorders and vice versa, in patients with AHI $\geq 30/h$ and relatively small LA, the risk was low (Table 3 and Figure 2).

Clinical Relevance of CSR in Heart Failure

Early observations indicated an association between CSR and heart failure,^{1,2} although not all patients with heart failure have CSR. One determinant of the variable occurrence of CSR in heart failure may be the severity of ventricular dysfunction; however, a clear and unequivocal correlation between the degree of ventricular dysfunction and the severity of CSR has not yet been demonstrated,⁵ indicating that other factors may be responsible for the occurrence of CSR in patients with CHF.

Theoretical modeling indicates that instability of respiratory control may play a major role in the pathogenesis of CSR.¹⁶ In the setting of heart failure, this instability may be related to several factors that might contribute to the occurrence of this respiratory pattern, including reduced body stores of CO₂ and O₂, hyperventilation arising from pulmonary vagal afferent stimulation from pulmonary venous congestion, prolonged circulation time, changes in resistance of the upper airways, instability of baroreflex control (which could affect respiratory control as well), and individual variability in the apneic threshold for CO₂ and in the ventilatory response to hypercapnia (central controller gain).^{5,17,18} The pathophysiological key to CSR in CHF is a tendency to hyperventilate, causing Pco₂ to fall below an apneic threshold, triggering recurrent central apneas.¹⁷ Once periodic breathing is initiated, Pco₂ oscillates above and below the apnea threshold during hyperpnea and apnea, respectively. Wakeful hypocapnia, due to hyperventilation or to the use of diuretic agents, has been suggested to be a critical factor in predisposing patients to develop CSR.

In our study, we did not find any difference in wakeful arterial Pco₂ of patients with AHI $\geq 30/h$ compared with those with AHI $< 30/h$ (Table 4). On the contrary, our patients with AHI $\geq 30/h$ showed lower arterial oxygen tension, suggesting an impaired ventilation/perfusion relationship arising from pulmonary hypertension and interstitial edema, thus the result of a more pronounced congestion. Although we did not find linear correlations between specific values of AHI and ejection fraction or deceleration time, patients with AHI $\geq 30/h$ generally had a more depressed ejection fraction and a shorter transmitral Doppler deceleration time of early filling as an index of restrictive diastolic filling, which has been demonstrated to be highly correlated with elevated filling pressure.¹² These findings confirm that this nocturnal breathing disorder arises secondary to heart failure and suggest that it is related to the severity of the disease. Importantly, our results indicate that its presence can have still further adverse consequences and an additional negative impact on prognosis (Figure 2). LA area proved to be the second independent predictor of mortality. It is possible to speculate that LA area affects survival probably because, over time, it reflects the

hemodynamic evolution of the heart and is more an expression of the progression of the failing heart than the actual atrial pressure and the degree of congestion.

CSR and the Autonomic Nervous System

CSR can have detrimental effects on cardiac function by inducing both hemodynamic changes and sympathetic overactivity. The sympathetic nerve traffic increases progressively throughout the period of central apnea, because combined hypoxia and hypercapnia have a synergistic effect on both the respiratory chemoreceptors and central sympathetic neurons.¹⁹ During the hyperpneic phase, the inspiratory effort, combined with hypoxia, is a factor that provokes arousals from sleep at the peak of hyperventilation²⁰ and hinders the transition to deep sleep and the restoration of nocturnal vagal tone.²¹ Thus, hypercapnic hypoxia and arousals from sleep result in sympathetic overactivity with surges of catecholamine release: overnight urinary norepinephrine and daytime plasma norepinephrine concentrations are markedly higher in patients with CHF and CSR than in similar CHF patients without CSR and are directly related to the frequency of arousals from sleep and degree of hypoxia but not to left ventricular ejection fraction.³ In other words, CSR can trigger sympathetic activation in some patients with CHF, so that the increased sympathetic drive is not simply a compensatory response to low cardiac output but may be related at least in part to the sleep disorder.

Although we did not directly assess neurohumoral activation, patients with AHI $\geq 30/h$ had evident autonomic abnormalities, as demonstrated by the phenylephrine test and heart rate variability analysis. They had, indeed, an impaired arterial baroreflex gain, expression of impaired vagal efferent nerve traffic response to baroreceptor stimulation.²² Moreover, both in the 24-hour period and during the night, they also showed a reduction of both sdNN (which reflects all the cyclic components responsible for variability) and pNN50 (which reflects the high-frequency component of variability, ie, those vagally mediated) as expressions of a lack of responsiveness of the sinus node to neural inputs and of a withdrawal of parasympathetic tone in conditions of marked sympathoexcitation.²³ Although it is possible to argue that the majority of these alterations may be related to the condition of heart failure per se, BRS was the best predictor of the AHI. Furthermore, preliminary data from our laboratory suggest that the improvement in BRS parallels AHI improvement over time, independently of ejection fraction.²⁴

Because sympathetic overactivity aggravates myocardial injury and affects prognosis, the available data suggest that CSR is part of a vicious circle whereby CHF leads to CSR, which provokes greater activation of the sympathetic nervous system, which, in turn, aggravates cardiac failure. Thus, the sympathetic nervous system may be the link between CSR and prognosis.

Limitations of the Study

We investigated the prognostic value of nocturnal breathing disorder in a group of clinically stable patients with CHF due to ischemic or primary cardiomyopathy while in sinus rhythm. Thus, our results are not necessarily applicable to all

patients with heart failure. Further investigations should be performed to assess the impact of nocturnal periodic breathing on survival in patients with other forms of cardiomyopathies and/or in atrial fibrillation.

We did not conduct a formal polysomnographic study, because the sleep study was performed by means of an unattended system that only provided information about the respiratory pattern and oxygen saturation. Thus, no information was available about sleep architecture and arousals. However, the characteristics of sleep were not the aim of the study, and a high correlation between the apneic events and arousals has already been documented.³ We used the unattended system because of its easy applicability, and the results of our study indicate that this form of sleep study should be performed in all CHF patients (particularly among those with an enlarged LA) to identify which of them have nocturnal breathing disorders.

The use of a single sleep study to assess prognosis has some limitations because the breathing pattern may change during the follow-up period, mainly because of the long-term effect of medical therapy for heart failure. Despite the dynamic nature of periodic breathing, our data indicate that patients with AHI ≥ 30 /h should be considered at higher risk for adverse outcome whenever this breathing disorder is documented. Serial follow-up sleep examinations are needed to provide further insights into the complex breathing dynamics during sleep and to investigate whether a reversible respiratory disorder with long-term medical therapy for heart failure or with specific treatment for CSR (continuous positive airway pressure or oxygen supplements) may predict (or be associated with) a more favorable prognosis.

Conclusions

The AHI is a powerful independent predictor of poor prognosis in clinically stable patients with moderate to severe CHF. The presence of a high AHI (≥ 30 /h) as an expression of severe breathing disorder adds prognostic information compared with other clinical, echocardiographic, and autonomic data, and it identifies patients at very high risk for subsequent cardiac death.

Because breathing disorders are generally underdiagnosed in the CHF population, our results indicate that more attention should be devoted to their diagnosis in this setting.

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