Heart Failure

Sleep and Exertional Periodic Breathing in Chronic Heart Failure
Prognostic Importance and Interdependence

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Background—Sleep and exertional periodic breathing are proverbial in chronic heart failure (CHF), and each alone indicates poor prognosis. Whether these conditions are associated and whether excess risk may be attributed to respiratory disorders in general, rather than specifically during sleep or exercise, is unknown.

Methods and Results—We studied 133 CHF patients with left ventricular ejection fraction (LVEF) ≤40%. During 1170±631 days of follow-up, 31 patients (23%) died. Nonsurvivors had higher New York Heart Association class, ventilatory response (Ve/VCO2 slope), and apnea-hypopnea index (AHI) and lower peak VO2 (all P<0.01); lower LVEF and prescription of β-blockers, and shorter transmtrial deceleration time (all P<0.05). Exertional oscillatory ventilation (EOV), established by cyclic fluctuations in minute ventilation that persisted for ≥60% of exercise duration with an amplitude ≥15% of the average resting value, was significantly more frequent in nonsurvivors (42% versus 15%, P<0.01). Multivariable analysis selected AHI (hazard ratio [HR] 5.66, 95% CI 2.3 to 19.9, P<0.01), peak VO2 (HR 0.93, 95% CI 0.90 to 0.97, P<0.01), and β-blocker prescription (HR 0.34, 95% CI 0.13 to 0.87, P<0.05) as predictors of cardiac events. The best cutoff for AHI was >30/h. EOV was significantly related to AHI >30/h (χ2 14.6, P<0.01); 78% of EOV patients showed AHI >30/h. Multivariable analysis, including breathing disorders alone (EOV, AHI >30/h) or in combination (EOV plus AHI >30/h), selected combined disorders as the strongest predictor of events (HR 6.65, 95% CI 2.6 to 17.1, P<0.01).

Conclusions—In CHF, EOV is significantly associated with AHI >30/h. Although each breathing disorder alone is linked to total mortality, their combination has a crucial prognostic burden. (Circulation. 2006;113:44-50.)

Key Words: heart failure ■ sleep ■ prognosis ■ exercise ■ ventilation

Overstated sympathetic discharge causes chronic perturbations of the cardiovascular system in heart failure (CHF) that lead to a progressive instability of respiratory control. Periodic breathing, an abnormal oscillatory ventilation pattern that consists of cyclic hyperpnea and hypopnea, has been observed during exercise1 and sleep2 in CHF patients. Exertional oscillatory ventilation (EOV) during exercise is a slow, prominent, consistent rather than random fluctuation that may be evanescent or transient and can have several distinct patterns: It has been observed throughout the entire exercise protocol, or disappearing during early exercise, or only disappearing at peak exercise.3–5 Central sleep apnea (CSA), associated with Cheyne-Stokes respiration (CSR), is characterized by apneas and hypopneas alternated with periods of hyperventilation that have a waxing/waning of tidal volume.6 Although these 2 breathing disorders have been described and evaluated separately, the prevalence of EOV and CSA is similar,7–9 and both appear to be controlled by the same key feedback mechanism, given the hypersensitivity to the partial pressure of carbon dioxide (PaCO2) and an augmented ventilatory drive, due to altered cardiopulmonary reflex control.10–12 Hypothetically, EOV and CSA in combination should alert the physician to the need to intensify medical therapy and careful surveillance, and separately, they herald poor prognosis.7–8,13 Thus, potentially, EOV and CSA may be interrelated, being signs of severe neuroautonomic derangement of the ventilatory control system, and clinically, their combination may be considered as an additional prognostic warning. The aims of the present study were (1) to investigate the prognostic value of these breathing disorders,
either alone or in combination, and (2) to determine the relationship between EOV and CSA in stable CHF patients.

Methods

Study Sample
We prospectively studied patients with CHF due to ischemic or idiopathic dilated cardiomyopathy who were referred for functional status assessment and risk stratification and who were undergoing clinical evaluation, Doppler echocardiography, cardiopulmonary exercise testing (CPX), and sleep study. Eligibility criteria were as follows: (1) Echocardiographic left ventricular ejection fraction (LVEF) ≤40% and in stable condition with medical treatment for at least 1 month; (2) ability to perform CPX, stopped for fatigue or dyspnea, with a peak respiratory exchange ratio ≥1.05 to avoid inappropriate prognostic stratification due to poor motivation on the part of the patient; and (3) potential follow-up for at least 6 months from entry for surviving patients. Ineligibility criteria were (1) restrictive and obstructive ventilatory disorders (vital capacity and total lung capacity <80% of predicted value and forced expiratory volume in the first second [FEV1] <70% of predicted value), (2) a body mass index >30 kg/m², and (3) presence of obstructive events exceeding 5 episodes per hour at sleep study. The institutional Ethics Committee approved the study, and all patients gave written informed consent.

Echocardiography
Echocardiographic evaluation (Hewlett-Packard imaging system, model 77622-A) and sleep study were performed within 6±2 days of CPX in stable clinical and pharmacological conditions. Left ventricular volume, LVEF, end-diastolic left ventricular volume index, and mitral deceleration time of early ventricular filling (DT) were measured as described elsewhere.7

Cardiopulmonary Exercise Testing
CPX was performed on a cycle ergometer with a ramp protocol of 10 W/min and with breath-by-breath respiratory gas exchange measurements using a computerized metabolic cart (SensorMedics, Vmax29). Details of the test protocol have been published previously.7 To improve the physiological validity of peak oxygen consumption (V Ő2) in the presence of EOV,16 we recorded the mean value of V Ő2 during the last 60 seconds of the test. Predicted peak V Ő2 was determined with a gender-, age-, height-, and weight-adjusted and protocol-specific formula outlined by Wassermann and colleagues.17 The ventilatory anaerobic threshold was detected by the V-slope method.18 Minute ventilation (V̇E) was plotted against carbon dioxide production (V̇CO2), both obtained every 10 seconds of exercise and measured in liters per minute. The relationship V̇E versus V̇CO2 (V̇E/V̇CO2 slope) was calculated as a linear regression function, excluding the nonlinear part of the relationship after the onset of acidic drive to ventilation.19

EOV Description
EOV was visually determined by cyclic fluctuations in minute ventilation that lasted for >60% of the exercise duration and had an amplitude of >15% of the average amplitude of cyclic fluctuations at rest, according to Kremser et al. Briefly, V̇E measured at rest and during exercise was displayed on an expanded time scale, and the duration and amplitude (as a percentage of average resting value) of each oscillation were calculated. Then, the durations of fluctuations with an amplitude of >15% of the average amplitude of cyclic fluctuations at rest were summed (Figure 1).

Sleep Apnea Screening
Ambulatory sleep apnea screening, with recording of body position, eye and leg movements, cardiotochgraphy, nasobuccal air flow, chest and abdominal effort, and pulse oximetry, has been described elsewhere.15 Standard definitions were used to describe and score the sleep-related breathing disorders. Apnea was defined as cessation of airflow that lasted at least 10 seconds, CSA as the absence of flow and thoracoabdominal movements, and obstructive events as the absence of airflow in the presence of thoracoabdominal movements. Hypopnea was defined as ≥50% decrease in the sum of thoracoabdominal movements lasting ≥10 seconds, followed by a reduction in SaO2 of at least 4%.

Follow-Up and Documentation of End Points
Patients were followed up at the outpatient clinic of our hospital, and their status was determined from the medical records. The follow-up of those who did not attend their scheduled appointments was obtained by telephone interview of the patient, patient’s family, or primary care physician. The composite end point was death due to cardiovascular disease (sudden death, progressive heart failure–related death, acute myocardial infarction, and pulmonary embolism), and urgent heart transplantation (status I patients). Data from patients who survived to the end of the follow-up period or who died of non–cardiac-related causes or underwent heart transplantation (except for urgent status I patients) were evaluated as “censored.”

Statistical Analysis
Continuous data are expressed as mean±SD. Student’s t test for nonpaired values and ANOVA were used to compare the means of groups for quantitative variables, if appropriate. For qualitative variables, the χ² test with Yates’ correction or Fisher’s exact test, if necessary, was used. To identify clinical and echocardiographic, gas exchange, and ergonomic parameters related to EOV or the apnea-hypopnea index (AHI), a logistic regression analysis was performed. The variables that showed a significant association with outcome (P<0.05) at univariate Cox survival analysis were included in the regression analysis based on the Cox proportional hazard model (multivariate analysis).20 Cutpoint values for variables predicting outcome were generated with receiver operating characteristic curves at regular intervals, and the best threshold was automatically identified as the value that minimized the expression [(1–sensitivity)²−(1−specificity)²]. The area under the curve was obtained according to Hanley and McNeil.21 Survival was estimated by the product-limit Kaplan-Meier method. Differences between survival curves were tested with the log-rank χ² statistic. The level of statistical significance was set at a 2-tailed probability value ≤0.05. All calculations were performed with the SAS 6.12 system (SAS, Inc).

Results
From April 1997 to April 2003, 175 patients were screened. Of these, 42 patients were excluded because of LVEF >40% (n=3), peak respiratory exchange ratio <1.05 (n=5), restrictive and obstructive ventilatory disorders (n=4), or presence of obstructive events (n=30). Thus, 133 patients met the
 inclusion criteria; these patients’ demographic and clinical characteristics are shown in Table 1. Despite optimal medical treatment, including angiotensin-converting enzyme inhibitors (95%), digitalis (63%), diuretics (92%), antiarrhythmic drugs (8%), and β-blockers (53%), the majority of patients were in New York Heart Association (NYHA) functional class II to III (n=118). Although mean peak respiratory exchange ratio was 1.16, which supports the assumption of optimal subject effort, exercise capacity was severely impaired, reaching only 52% of the predicted value (%V̇O₂); moreover, the ventilatory anaerobic threshold was not identified in 37 patients (28%).

### Follow-Up and Prognosis

No patient was lost to follow-up, which lasted 1170±631 days. Two patients died of noncardiac causes (cancer) and 30 of cardiac causes: Sudden death (n=15), progressive heart failure (n=13), and myocardial infarction (n=2). Five patients underwent heart transplantation, and 1 of these was hospitalized for hemodynamic support and urgent heart transplantation (status I patients). Accordingly, 31 patients (23%) had major cardiac events (cardiac death or urgent heart transplantation). Actuarial 1- and 2-year survival rates were 91% and 85%, respectively.

Non-survivors compared with survivors had higher Ve/V̇CO₂ slopes and AHI (all with P<0.01), lower LVEF, shorter DT, higher NYHA class, and reduced peak heart rate (all with P<0.05). A reduced peak V̇O₂ and %V̇O₂ (P<0.01) was also observed in non-survivors. In addition, the percentage of patients treated with carvedilol was significantly lower in those who died (P<0.05). Finally, EOV was significantly more frequent in non-survivors (Table 1). Regarding breathing disorders, on the basis of receiver operating characteristic analysis, the best cutoff values for Ve/V̇CO₂ slope and AHI were ≥33 and >30/h (Figure 2), respectively. Total mortality was 38% and 15% (P<0.01) in patients with Ve/V̇CO₂ slope ≥33 and <33, 46% and 17% (P<0.01) in those with and without EOV, and 39% and 9% (P<0.0001) in those with and without AHI >30/h; the Kaplan-Meier survival curves are shown in Figure 3. Multivariable Cox proportional hazard analysis selected AHI (hazard ratio [HR] 5.66, 95% CI 2.3 to 19.9, P<0.01), peak V̇O₂ (HR 0.93, 95% CI 0.90 to 0.97, P<0.01), and β-blocker prescription (HR 0.34, 95% CI 0.13 to 0.87, P<0.05) as predictors of mortality; no index of breathing perturbations during exercise, EOV or Ve/V̇CO₂ slope, emerged as a predictor of mortality.

Total mortality was 9% in patients without either EOV or AHI >30/h, 17% in those with EOV alone, 31% in those

### Table 1.

<table>
<thead>
<tr>
<th>Total Population</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>133</td>
<td>102</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±10</td>
<td>58±11</td>
</tr>
<tr>
<td>Men</td>
<td>125 (94)</td>
<td>98 (96)</td>
</tr>
<tr>
<td>Cause of heart failure: Ischemic</td>
<td>85 (64)</td>
<td>66 (65)</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>118 (88)</td>
<td>91 (89)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.3±0.7</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>127 (95)</td>
<td>99 (97)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>123 (92)</td>
<td>93 (91)</td>
</tr>
<tr>
<td>β-Blocker (carvedilol)</td>
<td>71 (53)</td>
<td>60 (58)</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>134±44</td>
<td>130±43</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23±7</td>
<td>25±8</td>
</tr>
<tr>
<td>DT, ms</td>
<td>154±40</td>
<td>159±52</td>
</tr>
<tr>
<td>Peak VO₂, mL·kg⁻¹·min⁻¹</td>
<td>14.5±5.4</td>
<td>15.2±4.0</td>
</tr>
<tr>
<td>% Predicted peak VO₂</td>
<td>51±12</td>
<td>52±12</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>34±10</td>
<td>31±7</td>
</tr>
<tr>
<td>EO V</td>
<td>28 (21)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.16±0.09</td>
<td>1.17±0.09</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>78±12</td>
<td>78±11</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>124±21</td>
<td>126±21</td>
</tr>
<tr>
<td>Resting SBP, mm Hg</td>
<td>110±13</td>
<td>110±14</td>
</tr>
<tr>
<td>Peak SBP, mm Hg</td>
<td>141±27</td>
<td>145±23</td>
</tr>
<tr>
<td>AHI, n/h</td>
<td>29±11</td>
<td>21±7</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; LVEDVI, left ventricular end-diastolic volume index; DT, Doppler-derived early mitral deceleration time; RER, respiratory exchange ratio; HR, heart rate; and SBP, systolic blood pressure.

Data are expressed as mean±SD or No. (% of patients).
with AHI >30/h alone, and 54% in those with combined EOV and AHI >30/h (χ² 22.7, P<0.0001; Figure 4). Multivariable analysis, repeated to include all clinical manifestations of instability of respiratory control (EOV alone, AHI >30/h alone, their combination, and best cutoff value of V˙E/V˙CO₂ slope), selected combined breathing disorders (HR 6.65, 95% CI 2.6 to 17.1, P<0.01), peak V˙O₂ (HR 0.93, 95% CI 0.90 to 0.97, P<0.01), AHI >30/h alone (HR 3.7, 95% CI 1.5 to 9.5, P<0.01), and β-blocker prescription (HR 0.45, 95% CI 0.23 to 0.99, P<0.05) as predictors of outcome.

**Relationship Between Exertional and Sleep Periodic Breathing**

A severe sleep-disordered breathing pattern (AHI >30/h) was observed in 61 (46%) of the study sample, whereas EOV was detected in 28 (21%); 39 (29%) patients had AHI >30/h alone, 6 (4%) had EOV alone, and 22 (16%) had both breathing disorders (AHI >30/h and EOV). Although EOV was present in only 36% of patients with AHI >30/h, almost all EOV patients (22 of 28, or 78%) had AHI >30/h. Only 6 (8%) of the 72 patients without AHI >30/h (AHI ≤30/h) had EOV.

Compared with patients with AHI ≤30/h, patients with AHI >30/h had a significantly higher NYHA class (2.4±0.7 versus 2.2±0.5, P<0.05) and V˙E/V˙CO₂ slope (36±8 versus 31±8, P<0.01), lower peak V˙O₂ (13.7±3 versus 15.1±4 mL·kg⁻¹·min⁻¹, P<0.01) and peak HR (116±19 versus 130±21 bpm, P<0.01). EOV was more frequent in those with AHI >30/h (22% to 36% versus 6% to 8%, P<0.01). Logistic regression analysis selected EOV (OR 5.3, 95% CI 1.9 to 14.5, P<0.01) and NYHA class (OR 2.4, 95% CI 1.2 to 5.0, P<0.05) as predictors of AHI >30/h.

EOV patients compared with those without EOV showed a significantly higher NYHA class (2.6±0.7 versus 2.2±0.5, P<0.01), V˙E/V˙CO₂ slope (38±4 versus 32±8, P<0.05), peak respiratory exchange ratio (1.20±0.11 versus 1.13±0.11, P<0.05), and AHI index (39±12 versus 26±15 per hour, P<0.01) and a lower peak V˙O₂ (12.7±2 versus 14.9±4 mL/kg/min, P<0.05), resting and peak heart rate (72±11 versus 78±11 bpm, P<0.05 and 115±17 versus 125±21 bpm, respectively; P<0.05), and peak systolic blood pressure (133±19 versus 144±25 mm Hg, P<0.05). Moreover, DT was significantly shorter in EOV patients (139±50 versus 158±48 ms, P<0.05). Logistic regression analysis selected AHI >30/h (OR 14.6, 95% CI 2.2 to 15.9, P<0.01) as the only predictor of EOV.
Patients with combined breathing disorders (EOV plus AHI >30/h) compared with those with either AHI >30/h or EOV alone showed significantly lower peak VO2 and higher VE/VCO2 slope (Table 2). Clinical characteristics (including NYHA class) and echocardiographic parameters were similar in the 3 groups.

**Discussion**

In the current prospective study, a number of points deserve mention because they reinforce established data or contribute new insight. First, we confirmed that both exertional (EOV) and severe sleep periodic breathing (AHI >30/h) are frequent in stable CHF patients, but our finding of a higher incidence of the nocturnal phenomenon is original. Second, for the first time, we documented that although almost all EOV patients had AHI >30/h, which suggests an interconnection, EOV was present in only a minority of patients with AHI >30/h. Third, although underrepresented in the present CHF cohort, EOV alone appears to be associated with a fairly reassuring outcome. Fourth, we certified that all clinical expressions of respiratory control instability, ie, higher VE/VCO2 slope, AHI >30/h, and EOV, were linked to outcome in CHF in univariate analysis (confirming previous findings), but we originally stated that only AHI >30/h was selected at multivariate analysis. Fifth, an innovative prognostic hierarchy of periodic breathing can be postulated with an upgraded risk from EOV alone, through AHI >30/h alone, to combined breathing disorders (CBDs; EOV + AHI >30/h).

### Individual Breathing Disorders and Prognosis

Only 2 studies have delineated the prognostic value of EOV in CHF.7,8 We certified that EOV had additional prognostic impact in 323 CHF patients; total mortality of patients with EOV was 40%.7 Leite et al8 confirmed that EOV is a powerful predictor of mortality in 84 CHF patients who were candidates for cardiac transplantation; in that study, the 2-year mortality rate for EOV patients was 55%. Although the criteria adopted to define EOV were different, with a more liberal definition used in the study by Leite et al,8 both experiences corroborated that EOV is an independent risk index of cardiac events on multivariate analysis designed to control confounding variables. In the present study, we documented that EOV was associated with mortality on univariate but not multivariate analysis. Although total mortality rate according to EOV was comparable to previous experiences,7,8 the prognostic significance of EOV was lower than that of AHI >30/h, endorsing the greater predictive role of nocturnal breathing instability.

In small CHF cohorts,13,22,23 with 2 exceptions,24,25 CSA associated with CSR has been reported to affect survival. Hanly et al22 documented a 78% mortality rate in 16 CHF patients with CSR and NYHA class III; Lanfranchi et al13

**TABLE 2. Clinical, Echocardiographic, Sleep, Exercise, and Gas Exchange Data According to Presence of Breathing Disorders, Alone or in Combination**

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>EOV Alone</th>
<th>AHI &gt;30/h Alone</th>
<th>CBD</th>
<th>No BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±6</td>
<td>59±8</td>
<td>61±7</td>
<td>56±12</td>
</tr>
<tr>
<td>Men</td>
<td>6 (100)</td>
<td>36 (92)</td>
<td>20 (61)</td>
<td>63 (95)</td>
</tr>
<tr>
<td>Cause of heart failure: Ischemic</td>
<td>4 (67)</td>
<td>22 (56)</td>
<td>16 (72)</td>
<td>43 (65)</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>4 (67)</td>
<td>35 (89)</td>
<td>20 (61)</td>
<td>59 (89)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.6±0.5</td>
<td>2.3±0.5</td>
<td>2.7±0.5</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25±1</td>
<td>26±2</td>
<td>25±2</td>
<td>24±5</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>6 (100)</td>
<td>36 (92)</td>
<td>21 (65)</td>
<td>64 (96)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>5 (83)</td>
<td>37 (95)</td>
<td>21 (65)</td>
<td>60 (91)</td>
</tr>
<tr>
<td>β-Blocker (carvedilol)</td>
<td>4 (66)</td>
<td>24 (62)</td>
<td>9 (41)</td>
<td>34 (52)</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>135±43</td>
<td>127±40</td>
<td>145±52</td>
<td>133±44</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>21±6</td>
<td>24±9</td>
<td>21±9</td>
<td>24±7</td>
</tr>
<tr>
<td>DT, ms</td>
<td>148±70</td>
<td>160±46</td>
<td>136±45</td>
<td>133±44</td>
</tr>
<tr>
<td>Peak VO₂, mL · kg⁻¹ · min⁻¹</td>
<td>14.4±1</td>
<td>14.6±3</td>
<td>12.2±2</td>
<td>15.0±5*</td>
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<tr>
<td>% Predicted peak VO₂</td>
<td>52±6</td>
<td>51±10</td>
<td>45±8</td>
<td>52±14</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>30±8</td>
<td>33±7</td>
<td>40±8</td>
<td>30±8†</td>
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<tr>
<td>Peak RER</td>
<td>1.18±0.05</td>
<td>1.19±0.10</td>
<td>1.16±0.11</td>
<td>1.15±0.08</td>
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<td>Resting HR, bpm</td>
<td>79±15</td>
<td>76±12</td>
<td>70±10</td>
<td>80±12</td>
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<tr>
<td>Peak HR, bpm</td>
<td>136±11</td>
<td>119±21</td>
<td>109±13</td>
<td>130±30</td>
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<tr>
<td>Resting SBP, mm Hg</td>
<td>100±11</td>
<td>111±14</td>
<td>107±17</td>
<td>110±14</td>
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<tr>
<td>Peak SBP, mm Hg</td>
<td>133±13</td>
<td>143±28</td>
<td>132±10</td>
<td>144±24</td>
</tr>
<tr>
<td>AHI, n/h</td>
<td>21±7</td>
<td>42±7</td>
<td>44±10</td>
<td>17±8†</td>
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</table>

No BD indicates no breathing disorders. Other abbreviations as in Table 1. Data are expressed as mean±SD or No. (%) of patients.

*P<0.05; †P<0.01.
substantiated that AHI ≥30/h adds prognostic information compared with clinical (NYHA), echocardiography (LVEF, DT, end-diastolic left ventricular volume index, left and right atria dimensions), functional (peak VO₂), and autonomic parameters (heart rate variability, diurnal baroreflex sensitivity) in 62 CHF patients in NYHA class II-III; and Sin et al²³ reported that CSA with CSR confers an increased risk of death and cardiac transplantation in 66 CHF patients. Conversely, Andreas et al²⁴ certified no CSR prognostic significance in 36 CHF patients, and recently, Roebuck et al²⁵ confirmed that CSA had no repercussions on long-term prognosis in 78 patients with severe CHF assessed for heart transplantation. Different diagnostic criteria for CSA (ie, CSR lasting more than 20% of total sleep time²⁴ or AHI >5/h²⁵), study population recruitment (ie, CHF with LVEF <55%-²⁵), and supplemental therapy (ie, prescription of continuous positive airway pressure²⁵) may variously contribute to explain the abovementioned discrepancy in the outcome impact. The present study confirmed the prognostic role of CSA in a broader number of patients, almost half again the sum of those reported in previous single experiences, with a longer follow-up than in 3 of 5 past mortality studies¹³,²³,²⁴ and with a comparatively low total mortality rate because of up-to-date therapeutic options, including prescription of β-blockers (carvedilol) to 53% and spirironolactone to 34% of the patients studied. In this large-scale and optimally up-to-date therapeutic mix, the plant (respiratory muscles, rib cage, and lungs), and the autonomic centers.²⁹ An EOV and CSA association seems plausible because both are coupled with an advanced heart failure profile (lower peak VO₂, higher NYHA class and Ve/VO₂ slope) that labels an overstated sympathetic drive, leading to toxic effects of catecholamine excess on the vulnerable cardiopulmonary and circulatory system; thus, the enhanced sympathetic outflow and altered cardiopulmonary reflexes unify both conditions. On the other hand, the combination of CSA and EOV seems counterintuitive, because the latter, although present at rest, occurs during exercise, when nonmetabolic behavioral influences are at play,¹¹ and the outcome difference between CBD versus AHI >30/h alone (Figure 4) assigns specificity to each different form of periodic breathing.

Exertional and Sleep Periodic Breathing: Relationship and Prognosis

Nearly 1 in 2 of our stable CHF patients had severe sleep periodic breathing (AHI >30/h), and almost 1 in 4 had EOV; importantly, sleep fragmentation was present in 93% of EOV patients, as 22 of 28 had AHI >30/h, and 4 of the remaining patients had AHI ≥15/h to <30/h. On the other hand, only 36% of patients with AHI >30/h had EOV. In brief, the group of those patients who had EOV alone represented a very minor proportion, whereas 2 main subgroups of breathing disorders emerged: CBD and AHI >30/h alone. Moreover, a distinct hierarchy of periodic breathing disorders (alone versus combined) contributed to discriminate prognosis in CHF: EOV alone gave a more reassuring outcome, whereas AHI >30/h alone and CBD showed an increasing impact on survival. In summary, although most of the EOV predictive influence can be attributed to concomitant AHI >30/h, EOV can critically worsen the outcome of patients with AHI >30/h, making CBD a peculiarly ominous condition.

The mechanism coupling EOV and CSA is largely a matter of speculation. Pathophysiologically, hyperventilation and prolonged circulatory time underpin the development of CSA-CSR in CHF. Two mechanism of hyperventilation have been proposed: First, stimulation of pulmonary vagal afferent nerves by elevation in pulmonary pressures,²⁶ and second, upregulation of both central²⁷ and peripheral²⁸ chemoreceptors. The respiratory control instability model takes into account the controller (peripheral and central chemoreceptors), the plant (respiratory muscles, rib cage, and lungs), and the feedback delay (circulatory time), and in order of priority, enhanced chemoreflex gain and delay time have the greatest propensity toward producing periodic breathing.²⁹ As regards EOV, the mechanistic pathways envisage a link between left ventricular dysfunction, skeletal and respiratory muscle myopathy, and exercise hyperventilation (steeper Ve/VO₂ slope) and/or oscillation and suggest that peripheral abnormalities may promote hyperventilation by a reflex control.¹⁰ Overactivated ergoreceptors, responding to accumulated by-products of muscle metabolism and changes in local vascular peripheral conductance, may excessively stimulate the respiratory centers.²⁹,³⁰ An EOV and CSA association seems plausible because both are coupled with an advanced heart failure profile (lower peak VO₂, higher NYHA class and Ve/VO₂ slope) that labels an overstated sympathetic drive, leading to toxic effects of catecholamine excess on the vulnerable cardiopulmonary and circulatory system; thus, the enhanced sympathetic outflow and altered cardiopulmonary reflexes unify both conditions. On the other hand, the combination of CSA and EOV seems counterintuitive, because the latter, although present at rest, occurs during exercise, when nonmetabolic behavioral influences are at play,¹¹ and the outcome difference between CBD versus AHI >30/h alone (Figure 4) assigns specificity to each different form of periodic breathing.

Clinical Implications

The present findings suggest a complementary role of CPX and an ambulatory sleep apnea study in the risk assessment of periodic breathing in CHF. When AHI >30/h is detected, CPX allows the identification of the EOV subset, almost one third of the AHI >30/h population, who manifest a significantly higher risk than those with AHI >30/h alone. When EOV is observed, an ambulatory sleep apnea study is needed to exclude AHI >30/h (EOV alone), a singular situation that is associated with a better outcome than CBD.

Study Limitations

We defined EOV according to suggestions from the literature:² application of the prognostic implications of our findings to different arbitrary definitions of EOV is not warranted. In addition, we must acknowledge that the number of statistical tests performed and relatively modest sample size of the study population may potentially inflate type I error. Nevertheless, a more restrictive approach, which included in the predictive model only those parameters with P < 0.01 at univariate analysis, led to similar results. Only established prognostic indices in CHF (NYHA, LVEF, DT, peak VO₂, Ve/VO₂ slope, AHI, and β-blocker prescription) were included in the multivariate model, and thus, the importance of the parameters selected strengthens our findings. Finally, EOV alone comprised a sample of just 6 patients, which, although it certifies the relationship between EOV and AHI >30/h and although mean follow-up was adequate (803 ± 267 days), leads to a cautionary interpretation of the prognostic significance.
Conclusions
Exertional (EOV) and severe sleep periodic breathing (AHI >30/h) are frequent in stable CHF patients, and although each disorder alone has a significant impact on survival, AHI >30/h has a preeminent predictive role. Moreover, with regard to periodic breathing, a hierarchy of prognostic upgrading, from EOV through AHI 30/h to CBD, can be envisaged. Finally, because of the significant EOV and AHI >30/h interconnection, EOV could be helpful for the identification of CHF patients who should be prioritized for early sleep screening, whereas when AHI >30/h is detected, CPX allows the identification of EOV patients who manifest a significantly higher risk than those with AHI >30/h alone. If these results are confirmed in further observational trials, it would mean that periodic breathing manifestations, during exercise or sleep, and their combination should be taken into account in the daily decision-making algorithm for CHF patients and in guiding therapeutic options and close surveillance in the short term.

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Disclosures
None.

References
Sleep and Exertional Periodic Breathing in Chronic Heart Failure: Prognostic Importance and Interdependence

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