Oscillatory Breathing Patterns During Wakefulness in Patients With Chronic Heart Failure
Clinical Implications and Role of Augmented Peripheral Chemosensitivity

Piotr Ponikowski, MD, PhD; Stefan D. Anker, MD, PhD; Tuan Peng Chua, MD; Darrel Francis, MRCP; Waldemar Banasiak, MD, PhD; Phillip A. Poole-Wilson, MD, FRCP; Andrew J.S. Coats, DM; Massimo Piepoli, MD, PhD

**Background**—Oscillatory breathing patterns characterized by rises and falls in ventilation with or without periods of apnea (Cheyne-Stokes respiration [CSR]) or without true apneas (periodic breathing [PB]) commonly occur during the daytime in chronic heart failure (CHF). We have prospectively characterized patients with cyclical breathing in terms of clinical characteristics, indices of autonomic control, prognosis, and the role of peripheral chemosensitivity.

**Methods and Results**—To determine cyclical breathing pattern, power spectral analysis was applied to 30-minute recordings of respiration in 74 stable CHF patients. Analyses of heart rate variability and baroreflex sensitivity were used to assess autonomic balance. Peripheral chemosensitivity was assessed with the transient hypoxia method. We also determined whether the suppression of peripheral chemoreceptor activity (hypoxia or dihydrocodeine) would influence the respiratory pattern. Cyclical respiration was found in 49 (66%) patients (22 [30%] CSR, 27 [36%] PB) and was associated with more advanced CHF symptoms, impaired autonomic balance, and increased chemosensitivity (0.80 and 0.75 versus 0.34 L min⁻¹ %Sao2⁻¹, P<0.001, for CSR and PB versus normal breathing, respectively). Transient hypoxia abolished oscillatory breathing in 7 of 8 patients. Dihydrocodeine administration decreased chemosensitivity by 42% (P=0.05), which correlated with improvement in respiratory pattern. Cyclical breathing predicted poor 2-year survival (relative risk 9.41, P<0.01, by Cox proportional hazards analysis), independent of peak oxygen consumption (P=0.04).

**Conclusions**—An oscillatory breathing pattern during the daytime is a marker of impaired autonomic regulation and poor outcome. Augmented activity of peripheral chemoreceptors may be involved in the genesis of this respiratory pattern. Modulation of peripheral chemosensitivity can reduce or abolish abnormal respiratory patterns and may be an option in the management of CHF patients with oscillatory breathing. (Circulation. 1999;100:2418-2424.)

Key Words: respiration ■ heart failure ■ receptors

Cheyne-Stokes respiration (CSR) during sleep is common in chronic heart failure (CHF). The episodes of apnea with concomitant hypoxemia and arousal, which are characteristic features of CSR, may be associated with increased sympathetic activity and precipitate arrhythmias. A similar pattern of respiration during the daytime has been recently related to a poor outcome. Patients with compensated CHF also demonstrate an oscillatory breathing pattern characterized by cyclical rises and falls in ventilation without true periods of apnea (periodic breathing [PB]). The physiological basis and clinical importance of such breathing disorders in awake CHF patients have not been clearly established.

Augmented peripheral chemoreceptor activity in CHF may produce in some patients the expression of slow rhythms in heart rate. These oscillations in heart rate often coincide with similar rhythms in respiration. Increased peripheral chemoreceptor activity may result in an instability of cardiorespiratory control, which when coupled with impaired baroreflex sensitivity can lead to slow oscillations in blood pressure and respiration. Therefore, it is plausible to speculate on the role of peripheral chemoreceptor overactivity in the genesis of cyclical respiration in CHF.

The aim of the present study was to detect the prevalence and characteristics of patients with a cyclical breathing pattern (PB or CSR) during the daytime, in terms of clinical CHF severity and indices of autonomic balance. We have evaluated the role of peripheral chemosensitivity and the effects of its suppression in the genesis of PB/CSR.

Received September 4, 1998; revision received July 16, 1999; accepted July 29, 1999.
From Cardiac Medicine (P.P., S.D.A., T.P.C., D.F., P.A.P.-W., A.J.S.C., M.P.), Imperial College, National Heart & Lung Institute, London, UK; the Cardiology Department (P.P., W.B.), Clinical Military Hospital, Wroclaw, Poland; and Franz-Volhard-Klinik (S.D.A.), Charité, Campus Berlin-Buch, at Max-Delbrück-Centrum, Berlin, Germany.

Correspondence to Piotr Ponikowski, MD, PhD, Cardiac Medicine, National Heart & Lung Institute, Dovehouse St, London SW3 6LY, UK.

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Methods

Patients
All consecutive patients who attended our outpatient CHF clinic between August 1994 and June 1996 and met the following criteria were considered as candidates for the study: >6-month history of CHF due to idiopathic dilated cardiomyopathy or ischemic heart disease, clinical stability for >1 month, sinus rhythm, no signs of fluid retention, unchanged medication, and no acute coronary event within 6 months preceding the study. Exclusion criteria included pulmonary disease, significant renal dysfunction, diabetes mellitus, autonomic neuropathy, and treatment with β-blockers. The study protocol was approved by the local ethics committee.

Assessment of PB
Patients were studied in the morning (9 to 12 AM) and were asked not to smoke or drink caffeine on the study day. After a 20-minute period of supine rest in a quiet room, 30-minute recordings of a respiratory signal (mercury-in-silastic strain-gauge plethysmograph, Hokanson) were obtained. A strain gauge was positioned over the lower part of the chest to obtain a clear respiratory signal, visually checked, and adjusted according to the scale of the plethysmograph. The equipment was calibrated electronically before each test. Subjects breathed spontaneously and were asked to relax but not to fall asleep during tests. By this method, the volume changes of the rib cage were monitored, and the output signal reflected changes in lung volume. Continuous recordings of heart rate (ECG) and noninvasive blood pressure (Finapres, Ohmeda) signals were performed.

Stationary 20-minute recordings were selected, and to identify oscillatory respiratory patterns producing an amplitude modulation in the breathing signal, autoregressive power spectral analysis was applied to the respiratory time series with 15 as a model order. After power decomposition, the very-low-frequency (VLF) band (from 0.003 to 0.04 Hz) was identified. The occurrence of a discrete well-defined peak in the VLF band, >5% of total variability, was considered as evidence of a cyclical breathing pattern. PB was defined as a pattern of waxing and waning of ventilation without periods of apnea, and when periodic apnea was detected, this was classified as CSR. In every case of the presence of PB/CSR, the central frequency (Hz) of the VLF respiratory component was calculated to obtain the PB or CSR cycle length (seconds). Figures 1 and 2 present examples of CSR and PB, respectively.

Evaluation of Autonomic Balance
Stationary 20-minute periods of recording were selected, and autoregressive power spectral analysis was applied to the R-R interval and systolic blood pressure time series. The following spectral bands were identified: VLF, low frequency (LF, from 0.04 to 0.15 Hz), and high frequency (HF, from 0.15 to 0.40 Hz). Total power (TP, from 0 to 0.50 Hz) and the areas below each peak were calculated in absolute units (ms²) or as normalized units (nu, with VLF [%TP] as the percentage of TP and LF [nu], and HF [nu] as the percentages of the TP within the LF and HF bands, respectively, after the subtraction of the VLF component). Cross-spectral analysis was used to assess the relation between oscillations in respiration and R-R interval and systolic blood pressure within the VLF band.

Peripheral Chemosensitivity Evaluation
Peripheral chemosensitivity was assessed using the transient hypoxia method. Minute ventilation was measured breath by breath, and continuous monitoring of O₂ and CO₂ concentrations was performed (Amis 2000 mass spectrometer, Innovision). The patient, unaware of the timing of the test, breathed pure nitrogen for 2 to 8 breaths. This was repeated 10 to 15 times to provide a wide range of O₂ saturations from 75% to 100%, with 2-minute intervals of air breathing between exposures to allow O₂ saturation and end-tidal CO₂ to return to the patient’s baseline. Arterial O₂ saturation was measured with a pulse oximeter (model N-200E, Nellcor). The average of the 2 largest consecutive breaths that gave the highest ventilation after the hypoxic stimulus was used to calculate maximal ventilation. The peripheral chemosensitivity was expressed as the slope of the regression line relating ventilation to arterial O₂ saturation (in L · min⁻¹ · SatO₂⁻¹).

Effect of Suppression of Peripheral Chemoreceptors on Cyclical Breathing

Transient Hypoxic Deactivation of Peripheral Chemoreceptors
Eight patients with a reproducible cyclical respiratory pattern underwent a 3-phase protocol (20-minute phases) during which they breathed room air (phase I), 100% O₂ delivered via mask (60% O₂ concentration in breathing air, phase II), and finally room air (phase III). During the protocol, respiration was recorded, and stable 15-minute periods at the end of each phase were selected and subjected to spectral analysis.

Effect of Dihydrocodeine on Cyclical Respiration
We have previously reported that dihydrocodeine decreases peripheral chemosensitivity in CHF. Eight patients with a cyclical respiratory pattern received placebo or dihydrocodeine (1 mg/kg body wt) on 2 separate days in a randomized double-blind design. One hour later, a 30-minute recording of the respiratory signal followed by the assessment of peripheral chemosensitivity was performed.
Statistical Analysis
Data are given as mean ± SD. The natural log of the components of heart rate variability (HRV) and peripheral chemosensitivity were computed to correct for a skewed distribution. The Student paired t-test and ANOVA with the Fisher post hoc test were performed as appropriate. Survival analysis was performed by use of the Cox proportional hazards model. Kaplan-Meier cumulative survival curves were constructed and compared using the Mantel-Haenszel log-rank test. A value of P < 0.05 was considered significant.

Results
We prospectively identified 92 suitable patients for the study, and 74 were enrolled (Table 1). The reasons for exclusion were unwillingness to participate (n=14) or technical problems in the analysis of respiratory data (n=4).

Clinical Characteristics of Patients With Oscillatory Breathing Patterns
Forty-nine (66%) CHF patients demonstrated a cyclical pattern of respiration. The mean central frequency of this peak was 0.022±0.007 Hz (range, 0.007 to 0.041 Hz), which corresponded with a mean cycle length of cyclical breathing of 50±21 seconds (25 to 143 seconds). Among these patients, in 22 (30% overall) a CSR-like pattern (central frequency 0.020±0.008 Hz) was observed (Figure 1), whereas the remaining 27 (36% overall) had a PB pattern (central frequency 0.024±0.006 Hz) (Figure 2).

Autonomic Balance in Patients With Cyclical Breathing
Patients from all 3 groups had similar resting heart rates. There was no difference in HRV spectral components between patients with CSR and PB. Compared with the NB group, patients with cyclical breathing revealed a different HRV profile, characterized by a depressed LF component and a more predominant VLF rhythm (Table 2).

Values are number (percentage) of patients or mean ± SD. LVEF indicates left ventricular ejection fraction.

Table 1. Baseline Clinical Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Age, y</th>
<th>57±10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 70 (95%) Female 4 (5%)</td>
</tr>
<tr>
<td>Cause of heart failure</td>
<td>Ischemic heart disease 57 (77%) Idiopathic dilated cardiomyopathy 17 (23%)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I 3 (4%) II 41 (55%) III 28 (38%) IV 2 (3%)</td>
</tr>
<tr>
<td>LVEF, % (n=64)</td>
<td>25±10</td>
</tr>
<tr>
<td>Peak O2 consumption, mL · min⁻¹ · kg⁻¹</td>
<td>18.6±6.3</td>
</tr>
<tr>
<td>Treatment</td>
<td>ACE inhibitors 69 (93%) Diuretics 72 (97%) Digoxin 22 (29%)</td>
</tr>
</tbody>
</table>

The clinical data of patients with CSR, PB, or normal breathing (NB) are presented in Table 2. There was no difference in age, etiology, therapy, or cardiorespiratory function between these groups, apart from more severe symptoms (NYHA functional class) in patients with CSR and PB versus patients with NB (P < 0.05). Ambulatory 24-hour ECG monitoring was performed in 62 (84%) patients: 19 CSR, 23 PB, and 20 NB. Nonsustained ventricular tachycardia (3 consecutive ventricular ectopic beats with a rate >100/min lasting <30 seconds) was present in 10 (53%) CSR and 12 (52%) PB patients compared with 2 (10%) NB patients (P < 0.01).

We assessed whether a cyclical respiratory pattern coincided with the occurrence of the VLF rhythm in heart rate and blood pressure, defined as a distinct peak within the VLF band of the R-R interval spectrum and systolic blood pressure spectrum. Forty-eight patients (65%) had a VLF rhythm in HRV (96% CSR versus 78% PB versus 24% NB, P < 0.001), and 44 patients (62%) had a VLF rhythm in the systolic blood pressure spectrum (90% CSR versus 67% PB versus 32% NB, P < 0.05). Within the VLF band, 17 patients revealed a significant coherence (>0.5) between the oscillations in
respiration and R-R interval (Figure 3), and 15 patients revealed a significant coherence between respiration and systolic blood pressure (Figure 3).

Baroreflex sensitivity was assessed in 35 (47%) patients randomly chosen from the entire population: 12 CSR, 11 PB, and 12 NB. Patients with CSR and PB exhibited severely depressed baroreceptor activity compared with NB patients (Table 2).

### Respiratory Disorders and Prognosis

At the end of follow-up in July 1998 (mean follow-up 838 ± 315 days, >2 years in all who survived, 100% follow-up), there were 21 (28%) deaths (mean time to death 524 ± 366 days, range 13 to 1321 days). Eighteen patients (37%) with a cyclical respiratory pattern (12 PB and 6 CSR) died; 3 NB patients (12%) died. Univariate Cox proportional hazards analysis identified peak O₂ consumption <14 mL ·
kg⁻¹ min⁻¹ (P=0.03), NYHA class III or IV (P=0.008), and a cyclical respiration (relative risk 9.41, P=0.003), as predictors of 2-year survival. Multivariate analysis revealed that an abnormal breathing pattern was related to death independent of peak O₂ consumption (P=0.04) and NYHA class (P=0.06). The 2-year survival was 67% (95% CI, 54% to 80%) for patients who had cyclical respiratory pattern versus 96% (88% to 100%) among NB patients (P=0.008).

Peripheral Chemosensitivity and Cyclical Breathing

Peripheral chemoreflex was evaluated in 53 (72%) patients randomly selected from the study population: 15 CSR, 21 PB, and 17 NB. None was hypoxemic at baseline: arterial O₂ saturation values ranged from 96% to 100% (mean baseline saturation was 98.8%, 99.1%, and 99.3% for CSR, PB, and NB, respectively). Peripheral chemosensitivity was similar in patients with CSR and PB but significantly higher in those patients compared with NB patients (P<0.005 in both comparisons) (Table 2).

Effect of Transient Hyperoxic Deactivation of Peripheral Chemoreceptors on Cyclic Respiratory Pattern

In 8 patients with reproducible cyclical breathing who were acutely exposed to hyperoxia, hyperoxic conditions abolished the cyclical respiratory pattern in 7 patients, and when patients breathed room air again, CSR or PB was restored in 4 patients within 20 minutes (Figure 4).

Effect of Dihydrocodeine on the Cyclical Respiratory Pattern

There was a significant fall in peripheral chemosensitivity after dihydrocodeine administration compared with placebo (0.66±0.49 versus 0.31±0.21 L·min⁻¹·%Sao₂⁻¹, P<0.05). In 4 patients with PB after placebo, a normal respiratory pattern was restored after dihydrocodeine administration. In 2 patients who demonstrated CSR after placebo, dihydrocodeine administration resulted in changes in the respiratory pattern toward PB.

Discussion

The main findings of the present study are that an oscillatory respiratory pattern is not a surrogate of the severity of CHF but, rather, a marker of abnormal autonomic balance and reflex function. Augmented peripheral chemosensitivity may be an important factor in the genesis of the oscillatory breathing patterns in CHF. The potential importance of cyclical respiratory pattern during wakefulness as a predictor of an increased prevalence of ventricular arrhythmias and a poor outcome has been also demonstrated.

In CHF, sleep-related breathing disorders worsen the patients’ symptoms, deteriorate cardiorespiratory function, and unfavorably influence outcome. A similar cyclical respiratory pattern commonly occurs during daytime resting conditions and during exercise in patients with stable CHF. We and the others have linked cyclical breathing with slow oscillations within the cardiovascular system, suggesting the existence a slow cardiorespiratory rhythm in patients with CHF. Although PB or CSR during the daytime may carry an important clinical meaning, there are few studies investigating this phenomenon.

We found that a cyclical respiratory pattern during the daytime was common in patients with stable compensated CHF. We did not observe a significant difference in the
clinical parameters of patients with oscillatory breathing compared with patients with NB, apart from a higher NYHA class in the former group. However, we did not measure hemodynamic parameters; therefore, we could not exclude the possibility of more compromised hemodynamic status in those with PB/CSR.

Patients with PB and CSR had a similar incidence (∼50%) of nonsustained ventricular tachycardia on Holter recordings, which was significantly higher than that for patients with NB. The association between CSR at night, episodes of O₂ desaturation, and arrhythmogenesis in CHF has been documented. Because sleep studies were not routinely performed, we do not know how many patients also exhibited classic CSR with episodes of hypoxemia at night and whether this was a cause of the higher incidence of nonsustained ventricular tachycardia. However, in the present study, compared with PB, a CSR-like pattern was not associated with any further increase in the complexity and severity of ventricular arrhythmias, suggesting that the occurrence of cyclical breathing pattern (either genuine PB or CSR-like) may be a marker of an increased risk of ventricular tachycardia.

Another new finding of the present study was that the presence of the oscillatory breathing during daytime identified patients with poor outcome, independent of the clinical parameters. There are a few reports investigating the impact of sleep-related breathing disorders on prognosis, but these studies involved smaller numbers of patients and conflicting results. Recently, Andreas et al found that CSR during the daytime but not during sleep had an important prognostic value.

We used the analysis of HRV and blood pressure variability as a tool to investigate sympathovagal balance. Compared with patients with NB, patients with CSR and PB demonstrated a similar pattern of HRV characterized by a significant decrease in the power within the LF band. Six patients had undetectable power within the LF band of the HRV spectrum; all of them exhibited periodic respiration (2 CSR and 4 PB). Reduction of, or absence of, the LF component of HRV could be potentially caused by a severely reduced peripheral target responsiveness with concomitant impairment in baroreflex circulatory regulation or by the recently suggested reduced central rhythmicity in autonomic outflow. Although we are not able to conclude which of these mechanisms would act in patients with PB, our findings confirm the association of cyclical respiration with severe autonomic imbalance. The clinical importance of this relationship can be only a matter of speculation. It has been documented that in normal subjects and in patients with obstructive sleep apnea, hypoxia, hypercapnia, and arousal are associated with increased sympathetic drive. In CHF, sympathetic overactivity contributes to ventricular arrhythmias and is also an independent prognostic factor. Thus, there may be a link between oscillatory breathing and the increased incidence of ventricular tachycardia and poorer outcome via severe autonomic imbalance.

Classic CSR is often viewed as the consequence of the instability in the feedback system controlling ventilation. The following factors could be responsible for the oscillatory respiration in CHF: an increase in controller gain (increased sensitivity to arterial O₂ and CO₂ changes), reduction in system damping (a decrease in total body stores of O₂ and CO₂), and a delay in information transfer (circulation time between lungs and brain). The increased chemoreceptor drive may represent the high controller gain, whereby small changes in O₂ and CO₂ can result in inappropriate large alterations of the system output. Therefore, overactive peripheral chemoreceptors may be responsible for the generation of oscillatory breathing.

We have previously shown an importance of peripheral chemoreceptors in the genesis of the slow rhythms in heart rate and blood pressure. In the present study, we demonstrated peripheral chemoreceptors to be overactive in patients with CSR/PB, and in the physiological experiments, we showed the importance of peripheral chemoreceptors in the genesis of the oscillatory breathing patterns. Breathing with O₂ abolished the rhythmic oscillations in respiration, but these cyclical patterns emerged again when breathing normal room air. Supplemental O₂ therapy has been shown to reduce CSR during sleep and also to improve exercise capacity in CHF patients. The mechanisms of the favorable influence of O₂ have not been investigated in these studies, but an effect on peripheral chemoreceptors should not be neglected. Dihydrocodeine can reduce breathlessness and improve exercise tolerance in CHF, most likely by a reduction in chemosensitivity. In the present study, dihydrocodeine administration caused a decrease in peripheral chemosensitivity (∼40% versus placebo) with concomitant changes in the periodic respiratory pattern.

Another interesting finding is the lack of any significant difference in clinical parameters, autonomic indices, and peripheral chemosensitivity between CHF patients with PB and those with true CSR. We hypothesize that both oscillatory breathing patterns (PB and CSR) occurring during wakefulness in CHF patients represent 2 aspects of the same phenomenon (which could be referred to as cyclical respiration), with similar pathophysiological mechanisms involved. In agreement with this hypothesis, we found that in some patients PB or CSR could alternatively be present on consecutive visits (data not shown).

The fact that baroreflex response was not measured in all patients could be a potential limitation of the present study. However, patients with baroreflex assessment were randomly chosen from the entire population and did not differ in the clinical characteristics from the remaining patients.

In summary, cyclical respiratory patterns during wakefulness are common in stable CHF and carry important clinical information. They occur on the background of impaired autonomic regulation and appear to be associated with an increased prevalence of cardiac arrhythmias and a poorer outcome. Enhanced activity of peripheral chemoreceptors may be an important factor in their genesis. Modulation of peripheral chemosensitivity could be a therapeutic option in CHF patients with cyclical breathing.

Acknowledgments
Dr Ponikowski was supported by a research fellowship from the European Society of Cardiology; Dr Anker, by a postgraduate fellowship from Max-Dehbrück-Centrum, Berlin, Germany; Dr Francis, by the British Heart Foundation; Dr Coats, by the Viscount Royston Trust; and Dr Piepoli, by the Wellcome Trust.
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