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Cardiac Resynchronization Therapy Improves Central Sleep Apnea and Cheyne-Stokes Respiration in Patients With Chronic Heart Failure

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OBJECTIVES We studied the effects of cardiac resynchronization therapy (CRT) on heart failure (HF) patients with central sleep apnea (CSA).

BACKGROUND Patients with advanced HF often suffer from CSA with Cheyne-Stokes respiration. Cardiac resynchronization therapy improves myocardial function and exercise capacity in HF patients with conduction disturbances. The relationship between CRT and CSA is currently unknown.

METHODS Twenty-four patients (7 females; 62 ± 11 years) with HF, a reduced left ventricular ejection fraction (24 ± 6%), and left bundle branch block (QRS duration 173 ± 22 ms) received a CRT device. The number of apneas and hypopneas per hour (apnea-hypopnea index [AHI]) and minimal oxygen saturation (Sa_{O_2}min) were quantified by cardiorespiratory polygraphy. Fourteen patients showed CSA (AHI >5/h), and 10 patients had an AHI <5/h without CSA. Subjective sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI). Data were evaluated before and after 17 ± 7 weeks of CRT.

RESULTS In patients with CSA, CRT led to a significant decrease in AHI (19.2 ± 10.3 to 4.6 ± 4.4, $p < 0.001$) and PSQI (10.4 ± 1.6 to 3.9 ± 2.4, $p < 0.001$) without Cheyne-Stokes respiration and to a significant increase in Sa_{O_2}min (84 ± 5% to 89 ± 2%, $p < 0.001$). There was no significant change in AHI (1.7 ± 0.7 to 1.5 ± 1.6), PSQI (2.4 ± 0.5 to 2.6 ± 0.9), and Sa_{O_2}min (90 ± 2% to 91 ± 1%) in patients without CSA.

CONCLUSIONS Cardiac resynchronization therapy leads to a reduction of CSA and to increased sleep quality in patients with HF and sleep-related breathing disorders. This may have prognostic implications in patients receiving CRT. (J Am Coll Cardiol 2004;44:68–71) © 2004 by the American College of Cardiology Foundation

Patients with heart failure (HF) often present with central sleep apnea syndrome (CSA) and Cheyne-Stokes respiration, which is associated with increased mortality (1,2).

Treatment with continuous positive airway pressure ventilation may improve sleep disorders (3) and cardiac function (4), whereas pharmacologic therapy alone has only minor effects (5). Atrial overdrive pacing reduces the number of sleep apnea episodes in pacemaker patients without HF (6). Cardiac resynchronization therapy (CRT) improves the hemodynamic and functional status of HF patients with ventricular conduction delay (7,8) and may reduce cardiac mortality (9).

We conducted a prospective trial to study the effects of CRT on CSA with Cheyne-Stokes respiration in HF patients.

METHODS

Patients. Twenty-four consecutive patients were included in the study. Of these, 14 showed evidence of CSA and Cheyne-Stokes respiration. All patients presented with heart failure of New York Heart Association (NYHA) functional class III, were in a clinically stable condition for two months or more, and took optimized heart failure medication, including beta-blockers (n = 22), angiotensin-converting enzyme inhibitors (n = 23), diuretics (n = 23), spironolactone (n = 21), and digitalis (n = 17).

Cardiac resynchronization therapy was applied using left or biventricular pacing in an atrially triggered mode. No patient had a conventional indication for pacemaker therapy. Table 1 shows patient characteristics and pacemaker device configurations. Data were evaluated before and after 17 ± 7 weeks of CRT.

The study was conducted in accordance with institutional guidelines, and all patients gave written, informed consent.

Sleep evaluation. Sleep-related breathing disorders were established by an ambulatory overnight cardiorespiratory polygraph (Somnocheck, Weinmann, Germany), which records nasal/oral airflow, chest and abdominal wall movements, oxygen saturation, and heart rate. Central sleep apnea was defined by absent chest and abdominal wall motion and airflow for ≥10 s, Cheyne-Stokes respiration by periodic occurrence of apnea and hyperventilation, and hypopnea by a reduction in respiratory airflow of >50% for ≥10 s, associated with desaturation >3%. The average number of episodes of apnea and hypopnea per hour (apnea-hypopnea index [AHI]) was determined. A "sleep-

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Abbreviations and Acronyms

AHI = apnea hypopnea index
CRT = cardiac resynchronization therapy
CSA = central sleep apnea
HF = heart failure
LV = left ventricular
NYHA = New York Heart Association
PSQI = Pittsburgh Sleep Quality Index
SaO_2min = minimal oxygen saturation
V_E/V_{CO_2} = slope of increase in ventilation relative to carbon dioxide production
V_{O_2} = oxygen consumption

related breathing disorder" was diagnosed if the AHI was >5/h (10).

The Pittsburgh Sleep Quality Index (PSQI), a retrospective self-rating questionnaire, measures the sum score of sleep quality of the last month (11). "Good" sleepers show a global PSQI sum score <5.

Exercise capacity, ventilatory response, and echocardiography. Cardiopulmonary exercise testing was performed on a bicycle ergometer using a ramp increment of 10 W/min. Oxygen consumption (V_{O_2}) was determined by breath gas analysis (Jaeger Oxycon Alpha, Germany) at peak V_{O_2} in the terminal phase of exercise and at the anaerobic threshold. To analyze the ventilatory response to exercise, we calculated the slope of ventilation increase relative to carbon dioxide production (V_E/V_{CO_2} slope) during exercise.

The 6-min walk test was performed between two points of 45-m distance on a plane floor.

Biplane left ventricular (LV) end-diastolic and end-systolic volumes and ejection fraction were quantified according to the modified Simpson's rule by two-dimensional echocardiography.

Statistics. Continuous data are expressed as the mean value ± SD. Statistical analyses were performed with SPSS software (SPSS Inc., Chicago, Illinois).

The Wilcoxon signed-rank test was applied for paired comparisons before and during CRT. Unpaired data were compared by the Mann-Whitney *U* test. The chi-square test was used for nominal variables. Correlation between measures was calculated using the Spearman rank correlation. For statistical analysis, only complete data sets of single parameters were included. A value of $p < 0.05$ was considered significant for all comparisons.

RESULTS

Clinical response to CRT. During CRT, NYHA functional class improved from III to II in 8 patients with and in 5 patients without CSA, whereas it was unchanged in the remaining 11 patients.

Table 2 shows the results of cardiopulmonary exercise testing, 6-min walk test, and echocardiographic data.

The anaerobic threshold was indeterminable in two patients with and two without CSA. One patient of each group was unable to perform cardiopulmonary exercise testing due to noncardiac reasons. There was no correlation of AHI with parameters of exercise testing or echocardiography.

Sleep evaluation. The effects of CRT on AHI are shown in Figure 1 and on minimal oxygen saturation (SaO_2min) and PSQI in Table 3. Although the PSQI was reduced in all CSA patients, it was still >5 in two patients during CRT. There was a significant correlation between the improvement of AHI and PSQI ($r = 0.831$, $p < 0.05$) in patients with, but not in patients without CSA ($r = -0.13$, p = NS) during CRT.

There was no change in body mass index or medication and no weight loss or exercise training that could have influenced AHI in any patient during the study. No patient received supplemental oxygen or continuous positive airway pressure therapy.

DISCUSSION

In HF patients, increased LV filling pressures can lead to pulmonary congestion and activation of pulmonary vagal irritant receptors, provoking hyperventilation and hypocapnia. Central sleep apnea occurs when arterial carbon dioxide partial pressures fall below the apneic threshold. The cycle length of alternating periods of hypocapnia-induced apnea and reflex hyperventilation (i.e., Cheyne-Stokes respiration

Table 1. Baseline Patient Characteristics and Device Configuration

	All Patients (n = 24)	CSA (n = 14)	No CSA (n = 10)	p Value* (CSA vs. No CSA)
Male/female (n)	17/7	12/2	5/5	NS
Age (yrs)	62 ± 11	65 ± 11	60 ± 11	NS
Ischemic/nonischemic (n)	12/12	10/4	2/8	<0.05
QRS complex (ms)	173 ± 22	177 ± 28	168 ± 20	NS
Body mass index (kg/m^2)	25.3 ± 2.7	24.6 ± 3.3	26.5 ± 2.3	NS
Pacemaker/ICD (n)	4/20	3/11	1/9	NS
Lateral/anterior pacing site (n)	21/3	13/1	8/2	NS
BV/LV pacing (n)	22/2	12/2	10/0	NS
Programmed AV delay (ms)	113 ± 14	115 ± 15	110 ± 13	NS

*Mann-Whitney *U* test for numerical variables and chi-square test for nominal variables. Data are presented as the number of men/women or the mean value ± SD.

AV = atrioventricular; BV = biventricular; CSA = central sleep apnea; ICD = implantable cardioverter-defibrillator; LV = left ventricular.

Table 2. Effects of Cardiac Resynchronization Therapy on Exercise Capacity and Echocardiographic Parameters

		All Patients (n = 24)	CSA (n = 14)	No CSA (n = 10)	p Value (CSA vs. No CSA)
V_E/V_{CO_2} slope	Pre	34.9 ± 5.8 (n = 18)	36.7 ± 5.5 (n = 11)	29.4 ± 2.7 (n = 7)	<0.01
	CRT	30.2 ± 5.2* (n = 18)	30.6 ± 5.8* (n = 11)	28.8 ± 2.8 (n = 7)	NS
V_{O_2}-AT (ml/min per kg)	Pre	10.1 ± 1.8 (n = 18)	10.0 ± 1.9 (n = 11)	10.4 ± 1.6 (n = 7)	NS
	CRT	13.3 ± 3.1* (n = 18)	13.4 ± 3.1* (n = 11)	13.3 ± 3.4* (n = 7)	NS
Peak V_{O_2} (ml/min per kg)	Pre	12.8 ± 3.0 (n = 18)	13.1 ± 3.1 (n = 11)	12.3 ± 3.0 (n = 7)	NS
	CRT	16.7 ± 4.8* (n = 18)	17.1 ± 5.2* (n = 11)	16.2 ± 4.4* (n = 7)	NS
6-min walk test (m)	Pre	302 ± 130	307 ± 122	302 ± 152	NS
	CRT	386 ± 116*	409 ± 95*	387 ± 144*	NS
End-diastolic volume (ml)	Pre	255 ± 78	243 ± 77	263 ± 80	NS
	CRT	206 ± 88*	202 ± 85*	214 ± 92*	NS
End-systolic volume (ml)	Pre	193 ± 78	178 ± 61	209 ± 76	NS
	CRT	142 ± 76*	135 ± 69*	153 ± 91*	NS
Ejection fraction (%)	Pre	24 ± 6	25 ± 5	23 ± 7	NS
	CRT	34 ± 10*	35 ± 9*	33 ± 11*	NS

*$p < 0.05$ vs. before implantation (Pre). Data are presented as the mean value ± SD.
CRT = cardiac resynchronization therapy; CSA = central sleep apnea; V_E/V_{CO_2} = slope of increase in ventilation relative to carbon dioxide production; V_{O_2} = oxygen consumption; V_{O_2}-AT = V_{O_2} at anaerobic threshold.

[1]) is inversely proportional to cardiac output (12) and thus directly related to the severity of HF. A reduced LV function delays the circulation time between the lungs and the chemoreceptors (13) and increases the sensitivity of chemoreceptors, especially to carbon dioxide (14). The degree of carbon dioxide hypersensitivity is a major determinant of Cheyne-Stokes respiration (15). An increase in chemoreflex sensitivity is mirrored by an elevated ventilatory response to exercise in HF patients (16).

Our study is the first to show that CRT improves cardiac function and reduces the severity of CSA with Cheyne-Stokes respiration in HF patients with a ventricular conduction delay. A significant decrease in AHI and a significant increase in Sa_{O_2}min was observed during CRT without the application of noninvasive ventilatory support.

These beneficial effects could be explained by the CRT-related improvement in cardiac function. It has been shown that CRT leads to a more efficient LV contraction (17), accompanied by a reduction in functional mitral regurgitation (18). This may, in turn, result in reduced pulmonary congestion as a triggering factor of the reflex mechanisms responsible for Cheyne-Stokes respiration.

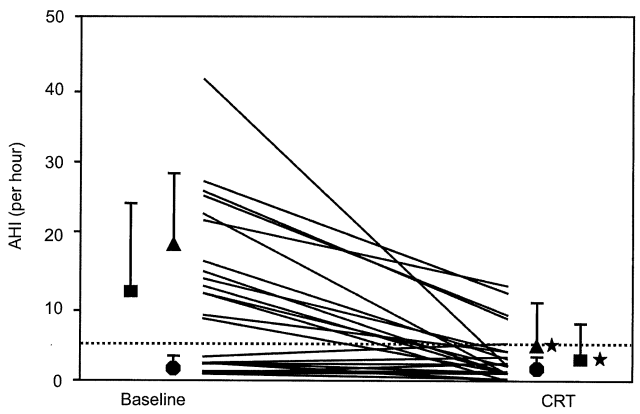

Figure 1. Effects of cardiac resynchronization therapy (CRT) on apnea hypopnea index (AHI) in patients with and without central sleep apnea (CSA). The **area under the dotted line** represents a normal AHI (<5). **Squares** = mean ± SD of all patients; **triangles** = mean ± SD of patients with CSA; **octagons** = mean ± SD of patients without CSA. **Stars** = $p < 0.005$ vs. baseline.

We also found a significant decrease in ventilatory response to exercise measured by the V_E/V_{CO_2} slope in CSA patients. This points to a reduction in circulation time between lungs and peripheral chemoreceptors, as well as a decrease in chemoreflex sensitivity to carbon dioxide. Therefore, our findings suggest that impaired LV function may be the primary cause of the reflex cascade, leading to Cheyne-Stokes respiration, and not vice versa.

Elevated V_E/V_{CO_2} slopes (19) and Cheyne-Stokes respiration (2) are associated with increased mortality in HF patients. Thus, the interruption of this vicious cycle of Cheyne-Stokes respiration may have a positive effect on prognosis.

Although the AHI is the result of a single-night evaluation, we could demonstrate positive long-term effects of CRT on sleep quality. The PSQI was significantly reduced and directly related to AHI improvement during CRT. These sleep-related effects might contribute to the significant improvement of patients' quality of life, as found in other CRT studies (7,8). Based on our findings, the improvement of CSA with Cheyne-Stokes respiration could be used as a helpful tool to evaluate the efficacy of CRT.

Breathing patterns, like respiration rate and minute ventilation, can be determined by implanted pacemaker sensors measuring the transthoracic impedance minute ventilation. Several studies have shown a high correlation between transthoracic impedance minute ventilation and actual minute ventilation measured by standard methods (20,21). Different breathing patterns and daily activities, including exercise testing, affect the transthoracic impedance minute ventilation (21) and allow one to draw conclusions about the patient's condition.

Therefore, analysis of breathing patterns may be used to determine the choice of CRT devices in the future. Patients

Table 3. Effects of Cardiac Resynchronization Therapy on Cardiorespiratory Polygraph and Pittsburgh Sleep Quality Index (PSQI)

		All Patients (n = 24)	CSA (n = 14)	No CSA (n = 10)	p Value (CSA vs. No CSA)
Cardiorespiratory polygraph					
Duration of recording (h)	Pre	8 ± 2	8 ± 2	8 ± 3	NS
	CRT	8 ± 3	8 ± 3	8 ± 2	NS
AHI (per h)	Pre	11.9 ± 11.7 (1–42)	19.2 ± 10.3 (9–42)	1.7 ± 0.7 (1–3)	0.00001
	CRT	3.3 ± 3.8* (0–12)	4.6 ± 4.4* (0–12)	1.5 ± 1.6 (0–4)	NS
Sa_{O_2}min (%)	Pre	88 ± 5 (70–92)	84 ± 5 (70–90)	90 ± 2 (88–92)	<0.05
	CRT	90 ± 2* (85–93)	89 ± 2* (85–90)	91 ± 1 (90–93)	NS
PSQI	Pre	7.5 ± 4.2 (2–14)	10.4 ± 1.6 (8–14)	2.4 ± 0.5 (2–4)	<0.05
	CRT	3.5 ± 2.2* (2–10)	3.9 ± 2.4* (2–10)	2.6 ± 0.9 (2–4)	NS

*$p < 0.001$ vs. before implantation (Pre). Data are presented as the mean value ± SD.
AHI = apnea hypopnea index; Sa_{O_2}min = minimal oxygen saturation; other abbreviations as in Table 2.

with CSA may benefit from devices with a minute ventilation sensor capable of analyzing specific breathing patterns. This would allow continuous and noninvasive monitoring of CRT efficacy.

Study limitations. We applied a single-night cardiorespiratory polygraphy, which is used for the initial ambulatory diagnosis of sleep apnea syndromes (22). Although polysomnography is regarded as the "gold standard," previous studies have shown a high diagnostic accuracy of the portable recording device (22).

Conclusions. In patients receiving CRT, the improvement of cardiac function and exercise capacity is associated with a significant improvement of CSA with Cheyne-Stokes respiration and sleep quality. Therefore, the analysis of breathing patterns could be used for device-based monitoring of CRT efficacy in the future. Further studies are necessary to evaluate the prognostic implications of breathing pattern analysis in HF patients receiving CRT.

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