Cardiac resynchronization therapy and atrial overdrive pacing for the treatment of central sleep apnoea

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Aims

The combined therapeutic impact of atrial overdrive pacing (AOP) and cardiac resynchronization therapy (CRT) on central sleep apnoea (CSA) in chronic heart failure (CHF) so far has not been investigated. We aimed to evaluate the effect of CRT alone and CRT + AOP on CSA in CHF patients and to compare the influence of CRT on CHF between CSA positive and CSA negative patients.

Methods and results

Thirty patients with CRT indication underwent full night polysomnography, echocardiography, exercise testing, and neurohumoral evaluation before and 3 months after CRT implantation. In CSA positive patients (60%), two additional sleep studies were conducted after 3 months of CRT, with CRT alone or CRT + AOP, in random order. Cardiac resynchronization therapy resulted in significant improvements of NYHA class, left ventricular ejection fraction, N-terminal pro-brain natriuretic peptide, VO_2max , and quality of life irrespective of the presence of CSA. Cardiac resynchronization therapy also reduced the central apnoea–hypopnoea index (AHI) (33.6 ± 14.3 vs. $23.8 \pm 16.9 \text{ h}^{-1}$; $P < 0.01$) and central apnoea index (17.3 ± 14.1 vs. $10.9 \pm 13.9 \text{ h}^{-1}$; $P < 0.01$) without altering sleep stages. Cardiac resynchronization therapy with atrial overdrive pacing resulted in a small but significant additional decrease of the central AHI (23.8 ± 16.9 vs. $21.5 \pm 16.9 \text{ h}^{-1}$; $P < 0.01$).

Conclusion

In this study, CRT significantly improved CSA without altering sleep stages. Cardiac resynchronization therapy with atrial overdrive pacing resulted in a significant but minor additional improvement of CSA. Positive effects of CRT were irrespective of the presence of CSA.

Keywords

Atrial overdrive pacing • Cardiac resynchronization therapy • Central sleep apnoea • Cheyne–Stokes respiration • Chronic heart failure

Introduction

Central sleep apnoea with Cheyne–Stokes respiration (CSA) is a common disorder with a prevalence of up to 40% in patients with chronic heart failure (CHF).^{1–3} Central sleep apnoea contributes to increased sympathetic nerve traffic, resulting in surges in blood pressure and heart rate, as well as a greater tendency to arrhythmia.⁴ Several studies indicate CSA as an independent predictor for mortality in

patients with CHF.^{4–6} Different treatment modalities have been evaluated, but a gold standard therapy has not yet been established for CSA.⁷

In 2002, Garrigue *et al.*⁸ observed a 50% reduction of central and obstructive sleep apnoea episodes by atrial overdrive pacing (AOP). These results could not be confirmed for obstructive sleep apnoea in several subsequent studies,^{9–12} but the effect of AOP on CSA has not been further evaluated so far. Cardiac resynchronization therapy (CRT) has been proposed as another potential therapeutic pacing

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approach for CSA, by recently published investigations.^{13–15} These studies, however, had significant methodological limitations. In two of the investigations, the results were obtained with ambulant polygraphy, which excludes analysis of sleep stages and is not the current gold standard diagnostic approach for sleep apnoea.^{14,15} The third study was weakened by the fact that of the 10 CSA positive patients investigated, three had significant coexisting obstructive sleep apnoea.¹³

Although the concept has not been proven, it has been suggested that both pacing modalities (AOP and CRT) may improve sleep apnoea mainly by augmenting cardiac output and therefore reducing pulmonary congestion and circulation delay with a consecutive reduction of hyperventilation and central events.^{15,16} Considering this concept, it is notable that we and others recently showed that CRT improves the blunted force–frequency relation in CHF patients.^{17,18} This implies that cardiac contractile function further improves with increasing heart rates in CHF patients during CRT. We therefore speculated whether atrio-biventricular overdrive pacing (AOP + CRT) could be advantageous over either AOP or CRT alone for the treatment of CSA in CHF patients.

Using a single-blinded, randomized, crossover design, we investigated the effects of 3 months of CRT alone and with the addition of acute nocturnal AOP (CRT + AOP) on the severity of CSA, sleep stages, and biomarkers in patients with severe CHF and indication for CRT. Furthermore, the effect of CRT on clinical and functional CHF status was compared between patients with and without CSA.

Methods

Patient selection

Patients aged >18 years with standard indication for implantation of a CRT device based on current guidelines¹⁹ were eligible for the study if they did not meet one of the following exclusion criteria: atrial pacemaker dependency, chronic atrial arrhythmias, inability to complete overnight sleep study as specified by the protocol, myocardial infarction, or coronary revascularization within two calendar months prior to enrolment, planned, or strong likelihood of cardiac surgery within 4 months following enrolment, obstructive lung disease as defined by a forced expiratory volume in one second/forced vital capacity <70% evidenced by spirometry, or a body mass index ≥ 30 kg/m². Written informed consent was obtained from each patient, and the study was approved by the University of Göttingen and University of Bonn Institutional Review Boards. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Protocol

The study protocol is shown in Figure 1. Before CRT implantation, patients underwent a baseline polysomnographic evaluation. Patients with a substantial proportion of obstructive events ($\geq 25\%$ of the apnoeas and hypopnoeas obstructive in type) were excluded from the study. An apnoea–hypopnoea index (AHI) ≥ 15 h⁻¹ was defined as CSA positive, whereas patients with an AHI <15 h⁻¹ were classified as CSA negative and served as the control group.³ The morning after the sleep evaluation, blood and urine samples were taken for further analysis of N-terminal pro-brain natriuretic peptide (NT-proBNP) in plasma and norepinephrine in urine and the patients were asked to complete the Minnesota Living with Heart Failure questionnaire as well as the Epworth Sleepiness Scale questionnaire. Additionally, an echocardiographic evaluation of left ventricular ejection fraction, left ventricular end-diastolic and end-systolic diameter, left atrial diameter, and right ventricular systolic pressure, estimated by

measurement of the systolic regurgitant tricuspid flow velocity and right atrial pressure, was performed. Furthermore, a cardiopulmonary exercise test for the determination of maximal oxygen uptake (VO₂max), maximum work, blood pressure, and exercise duration was also conducted.

Twelve weeks after implantation and biventricular pacing (pacing mode DDD with a lower rate limit of 45 min), all patients underwent a second echocardiographic evaluation and cardiopulmonary exercise test. The questionnaires were completed again and blood samples taken for NT-proBNP analysis. Furthermore, patients in the CSA positive group underwent two consecutive nights in the sleep laboratory with one night of CRT alone and one night of CRT combined with AOP, administered in randomized order. Atrial overdrive pacing was performed at 15 beats higher than the mean nocturnal heart rate of the preceding week, as derived from the device diagnostic memory. The programmed atrio-biventricular pacing rate was rounded to the closest 5, with an upper limit of 95 bpm. The morning after each night in the sleep laboratory, blood and urine samples were collected.

Polysomnography

An electroencephalogram, electrooculogram, electromyogram, and electrocardiogram were recorded as previously described.²⁰ Airflow was recorded by nasal pressure, while thorax and abdominal wall motion was monitored by RespiTrace (RespiTrace Systems, Ambulatory Monitoring Inc., NY, USA). Arterial oxygen saturation and partial pressure of carbon dioxide (pCO₂) were measured transcutaneously by pulse oximetry (Tosca, Linde Medical Sensors AG, Basel, Switzerland). The polysomnogram was visually analysed with a computer system (ALICE IV, Heinen und Löwenstein, Bad Ems, Germany) by two observers blinded to subject and intervention. An apnoea was considered obstructive when nasal flow was absent in the presence of abdominal or thoracic movements, and central when movements were absent as well. Central hypopnoeas were defined as a 50% or greater reduction in tidal volume from the baseline value for at least 10 s with proportional in-phase reductions in rib cage and abdominal movements. Obstructive hypopnoeas were similarly defined, except that out of phase thoracoabdominal motion had to be present.^{2,9} Sleep stages and arousals were evaluated according to standard criteria.^{21,22}

Biomarkers and cardiopulmonary exercise test

Following the night in the sleep laboratory, blood samples were taken each morning directly after waking, and urine was collected overnight. NT-proBNP was determined by an electrochemoluminescence immunoassay (Elecsys pro BNP sandwich immunoassay; Roche Diagnostics, Basel, Switzerland) and norepinephrine was measured by high-performance liquid chromatography and normalised to urinary creatinine. Cardiopulmonary exercise testing was conducted on a supine bicycle (Ergoscope, Ganshorn, Niederlauer, Germany). Testing began after collecting resting data for at least 6 min until the patients were in stable clinical condition. The patients were told to maintain a pedalling rate of 55–65 rpm. Starting with 10 W, work was increased by 10 W every minute to the point of exhaustion, while the patients were breathing room air through a mouthpiece. Blood pressure was measured every minute. VO₂max was evaluated and corrected for atmospheric pressure, temperature, and water vapour pressure.

Statistical analysis

Variables are given as mean $\pm$ SD. Data were analysed using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA). For comparisons of the baseline data and treatments (CRT vs. CRT + AOP), a two-sample t-test or a Fisher's exact test was performed, as appropriate. For

Figure 1 Flow chart showing study design. Patient enrolment and follow-up visit included polysomnography (PSG), physical examination, blood and urine samples, echocardiography, cardiopulmonary exercise test, device interrogation, and completion of questionnaires. Blood and urine samples were also collected the morning after PSG II and III. AHI, apnoea–hypopnoea index.

comparison of baseline to follow-up values, paired Wilcoxon signed rank tests were performed, and these were compared between CSA positive and negative patients using two-factor repeated measures ANOVA with an interaction term. Two-tailed tests were used and significance was recognized at a value of $P < 0.05$.

Results

Subject characteristics

From June 2005 to December 2006, a total of 44 patients were enrolled. Four patients were excluded after enrolment and baseline polysomnography because their obstructive component was too large. One patient was excluded from the study because of an incomplete baseline data set. Nine patients did not complete the study protocol and were thus not considered for the final data analysis. Causes were development of persistent atrial fibrillation ($n = 3$), death ($n = 1$), and withdrawal of consent ($n = 5$). Therefore, data from 30 patients (12 CSA negative and 18 CSA positive) were used for the final analysis.

Patient baseline characteristics are summarized in Table 1. None of the patients included had a previously diagnosed sleep apnoea. Significant differences between CSA negative and CSA positive patients were found for baseline left ventricular ejection fraction and AHI. CHF medication did not differ significantly between the groups. During the study period, diuretic medication was increased in one patient in the control (CSA negative) and one patient in the CSA positive group.

Heart rate and percentage of atrial pacing during cardiac resynchronization therapy and cardiac resynchronization therapy + atrial overdrive pacing nights

The mean nocturnal heart rate for the week preceding the two diagnostic sleep tests at follow-up was 65.6 ± 8.3 bpm. During the CRT nights, minimum heart rate of the CRT devices was programmed to 47.8 ± 4.8 bpm with a resulting percentage of atrial pacing of $10.2 \pm 26.5\%$. The latter was increased to $80.0 \pm$

Table 1 Baseline characteristics

	All patients (n = 30)	CSA negative (n = 12)	CSA positive (n = 18)	P-value
Sex (male/female)	27/3	11/1	16/2	n.s.
Age (year)	66.1 ± 9.8	66.2 ± 11.7	66.1 ± 8.6	n.s.
BMI (kg/cm ²)	27.1 ± 4.2	25.6 ± 2.5	28.1 ± 4.9	n.s.
ICM	7 (23.3%)	1 (8.3%)	6 (33.3%)	n.s.
LVEF (%)	22.2 ± 4.6	24.4 ± 3.6	20.7 ± 4.6	0.024
Heart rate	68.5 ± 12.7	68.0 ± 17.4	68.8 ± 8.9	n.s.
NYHA II	2 (6.7%)	1 (8.3%)	1 (5.6%)	n.s.
NYHA III	24 (80.0%)	11 (91.7%)	13 (72.2%)	n.s.
NYHA IV	4 (13.3%)	0 (0.0%)	4 (22.2%)	n.s.
AHI (h ⁻¹)	26.0 ± 18.2	8.0 ± 4.5	38.0 ± 12.9	<0.0001
VO ₂ max (mL/kg/min)	12.1 ± 3.0	13.0 ± 3.9	11.6 ± 2.1	n.s.
NT-proBNP (pg/mL)	4604 ± 6521	5210 ± 9836	4235 ± 3571	n.s.
Use of CHF medication				
β-blocker	29 (96.7%)	11 (91.7%)	18 (100.0%)	n.s.
ACE inhibitor/AT blocker	29 (96.7%)	11 (91.7%)	18 (100.0%)	n.s.
Diuretics	29 (96.7%)	11 (91.7%)	18 (100.0%)	n.s.
Spironolactone	21 (70.0%)	8 (66.7%)	13 (72.2%)	n.s.
Digitalis	18 (60.0%)	7 (58.3%)	11 (61.1%)	n.s.

For comparison of the baseline data, a two-sample t-test or Fisher's exact test where appropriate were performed.

BMI, body mass index; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; AHI, apnoea–hypopnoea index; VO₂max, maximum oxygen uptake; CHF, chronic heart failure.

29.4% during the CRT + AOP nights using a programmed lower heart rate of 84.1 ± 6.4 bpm.

Effect of cardiac resynchronization therapy on clinical, echocardiographic, and neurohumoral parameters in central sleep apnoea positive and central sleep apnoea negative patients

As shown in Table 2, 3 months of CRT resulted overall in an improvement of NYHA class, NT-proBNP, quality of life, left ventricular ejection fraction, and left ventricular end-systolic diameter, whereas the end-diastolic diameter remained unchanged when compared with the baseline value. On cardiopulmonary exercise testing, VO₂max, maximum systolic blood pressure, exercise duration, and maximum work were improved compared to baseline. There was no difference in improvement between patients with or without CSA with respect to the above-mentioned parameters except for maximum systolic blood pressure (Table 2). Of note, only CSA positive patients showed a significant improvement of maximum work, maximum systolic blood pressure, and exercise duration in the exercise test (Table 2).

Effect of cardiac resynchronization therapy and atrial overdrive pacing + cardiac resynchronization therapy on respiratory events in central sleep apnoea positive patients

Sleep characteristics of the CSA positive patients are summarized in Table 3. Three months of CRT resulted in a significant reduction

of the AHI, central AHI, apnoea index, and central apnoea index (Figure 2 and Table 3).

Combined use of AOP + CRT resulted in a small but significant additional decrease of the central AHI, hypopnoea index, and central hypopnoea index compared with CRT alone (Figure 2 and Table 3). No significant further improvement was observed during AOP + CRT, for the AHI, apnoea index nor the central apnoea index.

Effect of cardiac resynchronization therapy and atrial overdrive pacing + cardiac resynchronization therapy on sleep stages and ventilation in central sleep apnoea positive patients

Cardiac resynchronization therapy in CSA positive patients improved subjective sleep quality as assessed by the ESS questionnaire from 16.7 ± 2.9 to 14.8 ± 2.2 ($P < 0.01$). However, neither CRT alone nor CRT + AOP affected sleep stages in the polysomnography (Table 3). The same was noted for pCO₂ and mean and minimal nocturnal oxygen saturation (Table 3).

Effect of cardiac resynchronization therapy and atrial overdrive pacing + cardiac resynchronization therapy on biomarkers in central sleep apnoea positive patients

While CRT significantly reduced NT-proBNP and resulted in a trend towards a lower norepinephrine concentration in urine

Table 2 Differential effects of cardiac resynchronization therapy in central sleep apnoea negative and positive patients

	All patients			CSA negative	CSA positive	P CSA pos. vs. neg. ^b
	Baseline	Follow-up	P vs. baseline ^a	Δ change	Δ change	
VO ₂ max (mL/kg/min)	12.1 ± 3.0	13.8 ± 3.1	<0.001	1.4 ± 1.1	2.0 ± 2.4	n.s.
Exercise duration (s)	368.7 ± 180.1	468.2 ± 156.2	<0.0001	73.8 ± 141.2	133.9 ± 137.9	n.s.
Maximum work (W)	60.4 ± 24.2	75.0 ± 25.0	<0.0001	13.1 ± 32.5	17.7 ± 10.4	n.s.
Max SBP (mmHg)	137.3 ± 21.2	148.0 ± 18.4	<0.001	1.5 ± 13.3	16.1 ± 16.3	<0.05
Max DBP (mmHg)	86.5 ± 11.8	86.8 ± 12.9	n.s.	3.0 ± 10.9	−1.2 ± 15.2	n.s.
LVEF (%)	22.2 ± 4.6	29.8 ± 8.2	<0.0001	7.5 ± 7.8	7.7 ± 5.8	n.s.
LVESD (mm)	55.6 ± 9.6	51.8 ± 8.2	<0.05	−3.6 ± 8.2	−3.7 ± 6.3	n.s.
LVEDD (mm)	68.1 ± 8.9	66.9 ± 8.1	n.s.	−3.3 ± 7.8	−0.4 ± 5.4	n.s.
LA diameter (mm)	50.7 ± 7.1	48.1 ± 7.1	<0.01	−1.7 ± 2.4	−3.6 ± 5.2	n.s.
RVSP (mmHg)	31.0 ± 12.1	28.5 ± 13.2	<0.01	−3.0 ± 3.8	−2.1 ± 4.2	n.s.
MLHF questionnaire	46.6 ± 13.0	28.3 ± 13.0	<0.0001	−15.3 ± 12.6	−19.8 ± 15.0	n.s.
NYHA classification	3.1 ± 0.4	2.4 ± 0.6	<0.0001	−0.5 ± 0.7	−0.7 ± 0.8	n.s.
NT-proBNP (pg/mL)	4604 ± 6521	2706 ± 4872	<0.0001	−1792 ± 2567	−1841 ± 2117	n.s.

VO₂max, maximum oxygen uptake; MLHF, Minnesota Living with Heart Failure questionnaire; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; Max. DBP, maximum diastolic blood pressure; Max. SBP, maximum systolic blood pressure; LA, left atrial; RVSP, right ventricular systolic pressure.

^aWilcoxon signed ranks test.

^bTwo-factor repeated measures ANOVA with interaction.

Table 3 Effect of cardiac resynchronization therapy and atrial overdrive pacing in central sleep apnoea positive patients

	Baseline	CRT	CRT + AOP	P CRT + AOP vs. CRT
AHI (h^{-1})	37.1 $\pm$ 13.4	25.7 $\pm$ 17.5*	23.7 $\pm$ 17.9	0.07
oAHI (h^{-1})	1.4 $\pm$ 1.4	1.5 $\pm$ 1.4	1.7 $\pm$ 2.3	n.s.
cAHI (h^{-1})	33.6 $\pm$ 14.3	23.8 $\pm$ 16.9*	21.5 $\pm$ 16.9	0.009
AI (h^{-1})	18.0 $\pm$ 14.0	11.9 $\pm$ 14.2*	11.7 $\pm$ 15.0	n.s.
cAI (h^{-1})	17.3 $\pm$ 14.1	10.9 $\pm$ 13.9*	10.3 $\pm$ 14.2	n.s.
HI (h^{-1})	18.2 $\pm$ 7.3	13.7 $\pm$ 7.4	11.9 $\pm$ 6.8	0.025
cHI (h^{-1})	17.2 $\pm$ 6.9	12.9 $\pm$ 7.1	11.1 $\pm$ 6.6	0.013
TST (min)	382.1 $\pm$ 37.5	376.8 $\pm$ 41.6	380.0 $\pm$ 49.0	n.s.
S1 + S2 (%TST)	69.2 $\pm$ 8.5	69.0 $\pm$ 5.6	67.1 $\pm$ 5.3	n.s.
S3 + S4 (%TST)	8.9 $\pm$ 4.8	9.4 $\pm$ 2.7	10.4 $\pm$ 3.3	n.s.
REM (%TST)	22.1 $\pm$ 5.9	21.5 $\pm$ 6.5	22.5 $\pm$ 5.1	n.s.
SO ₂ mean (%)	89.9 $\pm$ 4.1	90.3 $\pm$ 3.4	89.9 $\pm$ 3.8	n.s.
SO ₂ min (%)	76.0 $\pm$ 9.9	78.4 $\pm$ 11.6	79.0 $\pm$ 13.2	n.s.
SO ₂ <90% (%TST)	7.9 $\pm$ 8.3	4.6 $\pm$ 5.5	4.8 $\pm$ 7.0	n.s.
pCO ₂ (mmHg)	43.2 $\pm$ 5.1	44.9 $\pm$ 4.4	45.4 $\pm$ 3.7	n.s.
NT-proBNP (pg/mL)	4235 $\pm$ 3571	1774 $\pm$ 1903**	1940 $\pm$ 2064	n.s.
NE (nmol/mmol Crea)	63.1 $\pm$ 142.2	32.2 $\pm$ 20.1	31.0 $\pm$ 18.7	n.s.

Wilcoxon signed ranks test besides CRT + AOP vs. CRT: two-sample t-test.

CRT, cardiac resynchronisation therapy; AOP, atrial overdrive pacing; AHI, apnoea–hypopnoea index; oAHI, obstructive AHI; cAHI, central AHI; AI, apnoea index; cAI, central AI; HI, hypopnoea index; cHI, central HI; TST, total sleep time; S1 + S2, sleep stages 1 and 2; S3 + S4, sleep stages 3 and 4; REM, rapid eye movement sleep; SO₂, oxygen saturation; pCO₂, partial pressure of CO₂; NT-proBNP, N-terminal pro-brain natriuretic peptide; NE, norepinephrine; Crea, creatinine.

*P baseline vs. CRT alone <0.01.

**P baseline vs. CRT alone <0.001.

Figure 2 Effect of cardiac resynchronization therapy (CRT) and atrial overdrive pacing combined with CRT (CRT + AOP) in CSA positive patients on the apnoea–hypopnoea index (AHI), central apnoea–hypopnoea index (cAHI), central apnoea index (cAI), and central hypopnoea index (cHI). P-value (Wilcoxon signed rank test) for the CRT compared with baseline revealed significance for the AHI, cAHI, and cAI ($P < 0.01$). P-value (two-sample t-test) for CRT + AOP compared with CRT revealed significance for cAHI ($P < 0.01$) and cHI ($P < 0.05$). * $P < 0.05$, ** $P < 0.01$.

($P = 0.08$) compared with baseline, neither NT-proBNP nor creatinine concentrations in urine were positively influenced by CRT + AOP when compared with CRT alone (Table 3).

Discussion

In this study, CRT resulted in a significant improvement in the severity of CSA, without improving sleep stages in patients with severe heart failure. The combined application of CRT and acute nocturnal AOP led to a further significant, but small improvement of CSA severity without influencing biomarkers compared with CRT alone. Another finding of the present study is that CRT improved the clinical and functional heart failure status and neuro-humoral and echocardiographic parameters of affected patients irrespective of the presence of CSA.

Effects of pacing on the severity of central sleep apnoea in central sleep apnoea positive patients

In CHF patients, the severely compromised cardiac function with elevated left ventricular filling pressures results in pulmonary congestion, causing activation of pulmonary J receptors, thereby inducing hyperventilation with hypocapnia, thus destabilizing ventilatory control and favouring CSA.²³ Improvement of cardiac function and reduction of pulmonary congestion by CRT might thereby directly improve CSA. Acute AOP during CRT may exert beneficial effects in a similar way. It has long been known that an increase in heart rate results in a positive inotropic effect on the heart. While this positive force–frequency relation is blunted in the failing human heart,^{24–26} we¹⁷ and others¹⁸ have recently demonstrated in patients with CHF an improvement of contractile function with increasing heart rates during CRT.¹⁷ Thus, an increase in heart

rate via AOP in addition to CRT will improve cardiac output and may thereby reduce the severity of sleep apnoea. However, in this study, we did not evaluate the acute haemodynamic effect of AOP during the CRT + AOP night. While different studies indicate a positive effect of CRT and AOP alone on the severity of CSA, the additional effect of AOP on top of CRT has not been investigated so far. Our study clearly demonstrates a substantial benefit of CRT on the severity of CSA confirming the positive effect previously described. Sinha *et al.*¹⁵ showed that CRT significantly reduced the AHI and improved oxygen saturation in the CSA positive group, as evidenced by ambulatory polygraphy. Similar data were found by Gabor *et al.*¹³ investigating 10 patients with CHF, CSA, and CRT. While approximately one-third of the patients also had obstructive sleep apnoea, CRT was shown to reduce central events. Recently, Oldenburg *et al.*¹⁴ conducted cardiorespiratory polygraphy in 36 patients with CSA, before and 5 months after CRT implantation, and showed similar effects in CRT responders.

An extra effect of short-term AOP on central hypopnoeas was also present in our study. However, this effect was small and does not seem to be clinically relevant. Garrigue *et al.*⁸ showed a significant reduction of CSA by AOP; however, this effect was observed in pacemaker-dependent patients and not resynchronization candidates with a severely reduced left ventricular ejection fraction and clear cut CSA. Furthermore, in our investigation, AOP was applied on top of CRT, whereas in the Garrigue study AOP was evaluated alone. Thus, it is possible that the minor effect in our study was weakened by the effect already achieved with CRT. The results of our study indicate, at most, an additive effect rather than a synergistic interaction of CRT and AOP. The small improvement indicates that AOP in addition to CRT is not an appropriate therapeutic approach to substantially reduce the severity of CSA and thus alleviate symptoms and improve transplant-free survival.²⁷

Effects of pacing on sleep stages in central sleep apnoea positive patients

In our study, sleep stages were neither affected by CRT alone nor by CRT and AOP, which confirms on the one hand that pacing *per se* has no negative effects on sleep. On the other hand, it also indicates that the improvement in respiratory events is not translated into an improvement of sleep stages. This is in line with the findings of Gabor *et al.*¹³ who were also unable to show an improvement in sleep stages evaluated via polysomnography. Despite these findings, in our study the Epworth Sleepiness Scale questionnaire showed a significant subjective improvement of sleep quality by CRT. This increase might be an expression of overall improvement of the general condition of the patients caused by CRT, rather than a specific effect of the improvement of sleep parameters. A similar improvement in sleep quality was reported by Sinha *et al.*,¹⁵ using the Pittsburgh Sleep Quality Index.

Neurohumoral activation in central sleep apnoea positive patients

Biomarkers of neurohumoral activation, such as plasma and urinary norepinephrine as well as BNP and NT-proBNP, the amino-terminal portion of the high molecular weight precursor of BNP, are elevated in CSA^{28,29} and are inversely correlated with left ventricular

function and prognosis in patients with heart failure.^{30,31} While previous studies have shown a positive effect of CRT on neurohumoral activation,^{32,33} an additional increase in heart rate due to overdrive pacing may further impact on systolic or diastolic left ventricular function and thus on these biomarkers. In the present study, NT-proBNP concentrations were significantly reduced by CRT. Cardiac resynchronization therapy reduced the mean norepinephrine concentration in urine by about 50% leading to a non-significant trend. Atrial overdrive pacing did not further influence urinary norepinephrine excretion or NT-proBNP concentration, suggesting that no major negative or positive additional effects on sympathetic activation or ventricular filling occurred.

Effects of cardiac resynchronization therapy in central sleep apnoea positive and central sleep apnoea negative patients

Cardiac resynchronization therapy is an established treatment modality for CHF patients with severely impaired left ventricular function and conduction delay.³⁴ Multiple positive effects of CRT on cardiac function, clinical variables, and mortality have been shown.³⁵ However, selection criteria are still not fully clear, as one-third of patients fail to benefit from CRT.³⁶ Central sleep apnoea may have negative consequences for the heart, caused mainly by sympathetic activation.²³ Treatment of CSA with continuous positive airway pressure results in a significant improvement of left ventricular ejection fraction in patients with severely impaired left ventricular function.⁵ The prevalence of CSA in CHF patients is considerably high.¹⁻³ Thus, one potential reason for the differences in response to CRT might be the concomitant presence of CSA. However, we were not able to show a difference in the effect of CRT between those patients with and those without CSA. Our results are in line with previously published data. Sinha *et al.*¹⁵ investigated 24 patients with CHF and CRT. Fourteen of these patients had concomitant CSA evidenced by ambulatory polygraphy. Improvement in echocardiographic and clinical parameters was not different between those patients with and those without CSA. Nevertheless, a possible indicator for the association outlined above might be the tendency to higher improvement characteristics of CSA positive compared with CSA negative patients in our study. However, differences were not statistically significant, which might be due to the small sample size investigated.

Limitations

Limitations include the single-blinded study design. In mitigation, this approach was adopted so as to maximize patient safety. Also, even though the data were obtained in a single-blinded fashion, quantification of sleep was made blinded to subject and intervention. Furthermore, no *in vivo* calibration of the transcutaneously evaluated variables (SO₂, pCO₂) was obtained. Also the results of our study are limited by the sample size. Finally, in this study, the acute effect of AOP was evaluated; the long-term effects of AOP during CRT and the prognostic implications of pacing strategies for the treatment of CSA in CHF patients remain to be determined.

Conclusion

This study provides further evidence, from full night polysomnography, that CRT significantly improves the severity of CSA. However, this improvement of CSA severity is not translated into an improvement in sleep stages. Acute, nocturnal AOP during CRT has a significant, but clinically not relevant, additional effect on CSA. Finally, the presence or absence of CSA did not influence the positive effect of CRT on CHF in this study. However, this finding needs further evaluation reflecting on the mutual interaction between the heart and CSA.

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