Long term biventricular resynchronisation therapy in advanced heart failure: effect on neurohormones

M U Braun, T Rauwolf, T Zerm, M Schulze, A Schnabel, R H Strasser

Objective: To assess prospectively the effect of cardiac resynchronisation therapy (CRT) on New York Heart Association (NYHA) functional class, cardiac function, cardiopulmonary exercise performance, and neurohormonal activation during 24 months’ follow up.

Design: Controlled study.

Patients and Results: 124 patients with severe congestive heart failure (ejection fraction < 35%, NYHA III–IV) and left bundle branch block (QRS duration > 150 ms) were enrolled (control group, n = 59; CRT group, n = 65) and followed up at 1, 3, 12, and 24 months. Compared with the control group, CRT led to significant short and long term improvements in functional NYHA functional class (mean (SEM) 2.1 (0.4) v 2.8 (0.4) at 24 months, p < 0.05), mean ejection fraction (25.7 (4%) v 21.1 (5%) at 24 months, p < 0.05), peak VO2 (16.8 (3.9) v 12.6 (3.5) ml/kg × min at 24 months, p < 0.01), and VO2 at anaerobic threshold (14.4 (3.7) v 10.8 (3.2) ml/kg × min at 24 months, p < 0.05). In addition, CRT for one and 12 months significantly decreased the plasma concentrations of noradrenaline (norepinephrine) and N-terminal fragment of pro-brain natriuretic peptide, whereas no changes were observed for other neurohormones such as antidiuretic hormone, aldosterone, and endothelin.

Conclusion: Long term CRT (≤ 24 months) results in significant improvement of NYHA class and cardiopulmonary exercise capacity and a short term decrease in neurohormonal activation.

Despite recent advances in pharmacological treatment for congestive heart failure (CHF), many patients remain symptomatic and continue to have a high mortality rate. About 25–30% of patients with severe cardiomyopathy experience an interventricular conduction delay, which evokes asynchronous ventricular contraction and is known to be an independent risk factor with poor long term prognosis. Cardiac resynchronisation therapy (CRT) has recently been proposed as an adjunctive treatment for these patients, improving acute haemodynamic function, contractile function, and clinical symptoms for up to 12 months, whereas data on longer follow up intervals have not been reported. Neurohormonal activation is one of the hallmarks of CHF and correlates with severity and prognosis of the syndrome. Inhibition of neuroendocrine systems by medical treatment specifically targeted at antagonising neurohormonal activation has yielded beneficial effects not only in clinical symptoms but also in survival. Only very few studies examined the influence of CRT on neurohormonal activation in CHF. Saxon and colleagues recently reported in a study of 53 patients that plasma noradrenaline (norepinephrine) concentrations were not significantly altered with biventricular pacing for 12 weeks compared with baseline. However, the effect of CRT on the plasma concentration of other neurohormones such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and endothelin have not been investigated.

Thus, the present study was performed to assess in patients with CHF with an interventricular conduction delay the effect of CRT over 24 months’ follow up on New York Heart Association (NYHA) functional class, systolic cardiac function, and cardiopulmonary exercise performance with a special focus on neurohormonal activation.

PATIENTS AND METHODS

Patient population

One hundred and twenty four patients with a left ventricular (LV) ejection fraction < 35% and a left bundle branch block (QRS duration of > 150 ms) were prospectively evaluated either in the control (n = 59) or CRT group (n = 65). Random assignment of patients to the control or the CRT group was greatly influenced by the rapidly increasing value of biventricular resynchronisation therapy during the past three years based on large, multicentre studies. Thus, at the beginning of the study (December 1999, when the data on CRT in patients with CHF were still preliminary and not verified by larger controlled studies) three patients declined CRT device implantation and preferred to continue taking optimal medical treatment, whereas later on five patients declined assignment to the control group and preferred CRT device implantation. Thus, about 92% of the patients were randomly selected and we took great care that the baseline parameters of both groups were comparable and similar. The LV synchronous contraction pattern was additionally verified by two dimensional colour Doppler echocardiography with three important aspects of interventricular and intraventricular conduction delay: aortic pre-ejection delay > 140 ms; interventricular mechanical delay (difference of the aortic pre-ejection delay and pulmonary pre-ejection delay) > 40 ms, and delayed activation of the posterolateral wall. All patients were in stable NYHA class ≥ III after receiving optimal medical treatment for ≥ 1 month, including angiotensin converting enzyme inhibitors, angiotensin II type 1 receptor blockers, and diuretics.

Abbreviations: ADH, antidiuretic hormone; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CARE-HF, cardiac resynchronisation in heart failure; CHF, congestive heart failure; COMPANION, comparison of medical therapy, pacing, and defibrillation in heart failure; CRT, cardiac resynchronisation therapy; ELISA, enzyme linked immunosorbent assay; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end systolic diameter; MIRACLE, multiSite InSync randomised clinical evaluation; MUSTIC, multiSite stimulation in cardiomyopathies; NT-proANP, N-terminal fragment of atrial natriuretic peptide; NT-proBNP, N-terminal fragment of brain natriuretic peptide; NYHA, New York Heart Association; VO2-AT, oxygen consumption at anaerobic threshold.
receptor antagonists, β blockers, spironolactone, digitalis, or diuretics. Owing to the clinical experience that many patients develop recurrent CHF symptoms after withdrawal of CHF standard medication and the potential to influence neurohumoral activation, the pharmacological treatment was not significantly changed during follow up. Patients with permanent atrial fibrillation and previously implanted pacemakers were excluded. All patients provided written and oral consent to the study protocol, which was approved by the institutional committee on clinical investigations. Three patients in the control group crossed over to CRT because of worsening of heart failure symptoms (two patients) or a documented episode of a sustained ventricular tachycardia (one patient), which was converted by electric defibrillation requiring an implantable cardioverter defibrillator. All three patients were excluded from the control group and from further analysis.

Baseline evaluation
At baseline a 12 lead surface ECG was recorded to determine PR interval and QRS duration. Systemic blood pressure was recorded. NYHA functional class was clinically evaluated.14 M mode, standard two dimensional transthoracic echocardiography (HP Sonos 5500, Hewlett Packard) was assessed to determine LV dimensions (left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD)), cardiac systolic function (LV ejection fraction), and mitral regurgitation.15 Participants underwent cardiopulmonary exercise testing according to a modified Naughton protocol16 to measure maximum treadmill exercise time, peak VO2, and VO2 at anaerobic threshold (VO2-AT). Gas exchange data were continuously recorded with an automated breath VO2, and VO2 at anaerobic threshold (VO2-AT). Gas exchange data were continuously recorded with an automated breath cardiopulmonary system (Oxycon A, Jaeger, Wuerzburg, Germany). Peak VO2 was defined as the highest consumption at anaerobic threshold.
Follow up results

Device related complications occurred in two patients (one LV lead dislocation, one major increase in the LV threshold) necessitating LV lead repositioning, which was performed successfully in both cases during a second intervention. The mean rate of biventricular pacing was >95% at each follow up, reporting a high frequency of active CRT. Systolic and diastolic blood pressures were not changed after the indicated follow up intervals. In the year before CRT device implantation (CRT group), 42 patients were hospitalised for heart failure due to LV lead instability (one patient) or an unacceptably high pacing threshold (one patient). Epicardial leads were surgically implanted with uneventful outcomes.

Cardiopulmonary exercise testing

As table 3 shows, the cardiopulmonary exercise parameters maximum exercise duration, peak VO₂, and VO₂-AT improved significantly in response to CRT during the longitudinal observation and compared with the control group at each follow up. Peak VO₂ and VO₂-AT increased from 3.9 (4.5) ml/kg × min and 11.1 (3.8) ml/kg × min at baseline to 17.1 (4.1) ml/kg × min and 13.3 (3.2) ml/kg × min after three months of CRT. This improvement persisted for up to 24 months of treatment, providing evidence for a long term benefit of CRT on cardiopulmonary exercise parameters in our patient population.

Effect of CRT on neurohormone activation

Neurohormone concentrations of noradrenaline, NT-proANP, NT-proBNP, ADH, aldosterone, and endothelin were determined at baseline and after one, 12, and 24 months of follow up (table 4). Compared with the control group and with baseline, CRT for one month and 12 months significantly decreased the plasma concentrations of noradrenaline and NT-proBNP and non-significantly lowered the concentration of NT-proANP. After 24 months of biventricular pacing, this beneficial and inhibitory effect of CRT on neurohormonal activation was partially reversed. No changes in the plasma concentration of ADH, aldosterone, and endothelin were observed in either group during follow up.

| Table 2 | QRS duration, NYHA class, and cardiac parameters at baseline and during follow up in the CRT and control groups |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control (n = 59) | CRT (n = 65) | Control (n = 58) | CRT (n = 65) | Control (n = 57) | CRT (n = 64) | Control (n = 62) | CRT (n = 64) |
| QRS duration (ms) | 175 (22) | 172 (19) | 182 (24) | 147 (14)* | 175 (20) | 150 (18)* | 179 (21) | 148 (17)* |
| NYHA class | 3.0 (0.6) | 3.1 (0.5) | 2.9 (0.4) | 2.3 (0.4)* | 3.0 (0.5) | 2.1 (0.3)* | 2.9 (0.4) | 2.2 (0.3)* |
| LVEDD (mm) | 69.3 (9) | 70.6 (10) | 68.8 (8) | 67.4 (9) | 70.1 (10) | 67.7 (10) | 69.6 (9) | 68.7 (11) |
| LVEDV (mm) | 58.9 (7) | 60.1 (8) | 61.7 (9) | 62.8 (8) | 60.3 (9) | 57.6 (7) | 59.7 (9) | 57.6 (7) |
| EF (%) | 21.5 (5) | 20.9 (4) | 20.9 (4) | 24.8 (4)* | 21.4 (6) | 26.2 (5)* | 20.7 (5) | 25.3 (4)* |
| MR grade | 1.7 (0.3) | 1.5 (0.6) | 1.6 (0.6) | 1.2 (0.5) | 1.4 (0.7) | 1.4 (0.5) | 1.6 (0.3) | 1.3 (0.6) |
| LA diameter (mm) | 42 (7) | 44 (6) | 41 (6) | 42 (4) | 44 (8) | 46 (6) | 47 (6) | 44 (7) |

Data are mean (SEM).

* p < 0.05 compared with control.

LA, left atrial; MR, mitral regurgitation.

| Table 3 | Cardiopulmonary exercise testing at baseline and during follow up in the CRT and control group |
|---|---|---|---|---|---|---|---|---|---|
| | Control (n = 59) | CRT (n = 65) | Control (n = 58) | CRT (n = 65) | Control (n = 57) | CRT (n = 64) | Control (n = 62) | CRT (n = 64) |
| Maximum exercise duration (s) | 458 (185) | 464 (172) | 494 (162) | 553 (194)* | 471 (192) | 573 (202)* | 455 (187) | 557 (188)* |
| Peak VO₂ (ml/kg × min) | 13.4 (4.0) | 13.9 (4.5) | 12.8 (3.0) | 17.1 (4.1)* | 13.1 (3.7) | 17.8 (4.2)* | 12.6 (3.5) | 16.8 (3.9)* |
| VO₂-AT (ml/kg × min) | 10.7 (3.2) | 11.1 (3.8) | 10.2 (3.3) | 13.3 (3.2)* | 11.5 (3.7) | 14.0 (4.1)* | 10.8 (3.2) | 14.4 (3.7)* |

Data are mean (SEM).

* p < 0.05 compared with control.
DISCUSSION

The main findings of the present controlled study are that CRT in patients with CHF and an interventricular conduction delay results in a significant long term (over 24 months) improvement of cardiac systolic function (as determined by LV ejection fraction) and cardiopulmonary exercise capacity including peak VO₂ and VO₂-AT. Additionally, we report an inhibitory short term effect of CRT on neurohormonal activation with a significant decrease of plasma noradrenaline and NT-proBNP after one and 12 months of biventricular pacing. This effect was diminished at the 24 month CRT follow up, suggesting that this improved neurohormonal status is most prominent in the early phase of CRT treatment and declines over time.

Two recently published, randomised, controlled trials (MUSTIC (multisite stimulation in cardiomyopathies) and MIRACLE (multisite InSync randomised clinical evaluation)) have shown a beneficial effect of CRT over six months of follow up on NYHA functional class, quality of life scores, and submaximal and maximum exercise capacity as well as a reduced hospitalisation rate.²⁶ Similar encouraging results were recently reported by Linde and colleagues²² and Gras and associates²¹ for up to 12 months of CRT. On the basis of our data this improvement in NYHA functional class and cardiopulmonary exercise parameters would persist over 24 months. These effects were associated with an increase in cardiac systolic function (as determined by LV ejection fraction), a decrease in cardiac dimensions (LVEDD and LVESD), and a sustained reduction of the paced QRS duration, suggesting that biventricular synchronisation is preserved for up to two years and may have an inhibitory effect on LV deterioration in the CHF remodelling process. Furthermore, hospitalisation and mortality were reduced in the present study during CRT compared with controls.

Owing to the limited number of patients enrolled in both groups we are aware that no final conclusion can be drawn regarding the influence of biventricular pacing on survival rates in CHF. The impact of CRT on mortality, which remains inordinately high in severe LV systolic dysfunction, is being investigated in the CARE-HF (cardiac resynchronisation in heart failure) and COMPANION (comparison of medical therapy, pacing, and defibrillation in heart failure) trials.

Activation of the neuroendocrine system is an early and compensatory mechanism in patients with CHF with LV dysfunction and has been recognised as a possible predictor of death.¹⁵ ²¹–²⁶ It is not known whether CRT in these patients with left bundle branch block may influence neurohormonal activation synergistically with medical treatment. Saxon and colleagues¹³ recently reported that the concentration of noradrenaline was not significantly altered during biventricular pacing for three months. In contrast, Hamdan and colleagues²⁷ found that CRT improved haemodynamic function and decreased sympathetic nerve activity, which closely correlates with the plasma noradrenaline concentration.²⁸ The present study confirmed these data with a significant decrease of noradrenaline and NT-proBNP after short term CRT, whereas this effect was attenuated after 24 months’ long term follow up. With respect to this background, a very recent study of Johnson and colleagues²⁹ showed that improved haemodynamic parameters (that is, pulmonary capillary wedge pressure and cardiac output) and ventricular loading in patients with CHF reduced neurohormonal activation with lowering of plasma concentrations of noradrenaline, ANP, and BNP. ANP and BNP are vasoactive peptides produced by atrial and ventricular myocytes and are released in response to chamber wall tension.¹⁵ As BNP is released from the myocardium of the ventricles, the NT-proBNP plasma concentration is a particularly sensitive marker of impending ventricular damage. Reduced BNP concentration may be related to improved LV systolic properties or filling pressures. The high baseline concentration of BNP in our study population relative to other studies of patients with CHF may be explained by the additional interventricular conduction disturbance that was the inclusion criterion reflecting ventricular desynchronisation.

Study limitations

This study, albeit prospective and controlled in design, was not randomised. On the basis of the recent encouraging data on CRT in patients with CHF with a left bundle branch block, several of our patients chose to have biventricular devices implanted during the course of the study. Nevertheless, the baseline values in both groups were close, indicating that their comparison is valid.

In summary, we have shown that CRT in patients with CHF with a left bundle branch block has a long term beneficial effect on NYHA functional class, cardiac systolic function, and cardiopulmonary exercise parameters, as well as an inhibitory short term effect on neurohormonal activation with a significant decrease in the plasma concentrations of noradrenaline and NT-proBNP after one and 12 months of biventricular pacing. However, this improvement was greatly attenuated after 24 months of CRT follow up, suggesting that this inhibitory effect of the neurohormonal status is most prominent in the early phase of CRT and decreases over time.

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*BOTH authors contributed equally to the work.

No financial support was received for the present study.

Table 4 Neurohormone concentrations at baseline and during follow up in the CRT and control groups

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 month</th>
<th>12 months</th>
<th>24 months</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>CRT</td>
<td>Control</td>
<td>CRT</td>
</tr>
<tr>
<td></td>
<td>(n = 59)</td>
<td>(n = 65)</td>
<td>(n = 58)</td>
<td>(n = 65)</td>
</tr>
<tr>
<td>Noradrenaline (nmol/l)</td>
<td>3.34 (1.44)</td>
<td>3.45 (1.31)</td>
<td>3.27 (1.29)</td>
<td>2.56 (1.05)*</td>
</tr>
<tr>
<td>NT-proANP (pmol/l)</td>
<td>1672 (922)</td>
<td>1786 (1003)</td>
<td>1793 (954)</td>
<td>1505 (879)</td>
</tr>
<tr>
<td>NT-proBNP (pmol/l)</td>
<td>1551 (917)</td>
<td>1502 (732)</td>
<td>1492 (869)</td>
<td>1178 (651)*</td>
</tr>
<tr>
<td>ADH (pmol/l)</td>
<td>9.5 (5.0)</td>
<td>6.9 (3.8)</td>
<td>7.7 (4.1)</td>
<td>6.7 (2.9)</td>
</tr>
<tr>
<td>Aldosterone (nmol/l)</td>
<td>0.30 (0.19)</td>
<td>0.25 (0.18)</td>
<td>0.24 (0.15)</td>
<td>0.21 (0.14)</td>
</tr>
<tr>
<td>Endothelin (pg/ml)</td>
<td>1.6 (0.9)</td>
<td>1.7 (0.8)</td>
<td>1.5 (1.0)</td>
<td>1.6 (1.1)</td>
</tr>
</tbody>
</table>

Data are mean (SD).

* p<0.05.

ADH, antidiuretic hormone; NT-proANP, N-terminal fragment of pro-atrial natriuretic peptide; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide.
REFERENCES


Electronic Pages

Electronic only articles are published in conjunction with this issue of Heart.

Acute myocardial infarction caused by a septic coronary embolism diagnosed and treated with a thrombectomy catheter

M Tanike, M Nishino, Y Egami, I Kondo, R Shutta, K Tanaka, T Adachi, J Tanouchi, Y Yamada, K Kawano

Acute myocardial infarctions are common in bacteremia but are seldom diagnosed during life. A 64 year old man with severe chest pain who had fever for several days due to possible bacteremia was shown by ECG and echocardiography to have possible lateral infarction. Immediate coronary angiography showed possible thrombus in the left circumflex artery, which was treated by thrombectomy catheter. Bacterial thrombus was removed and was verified by histological examination. A stent was implanted without complications. Acute myocardial infarction caused by septic embolism is usually fatal; however, thrombectomy may be useful in these cases.

(Heart 2005;91:e34) www.heartjnl.com/cgi/content/full/91/5/e34

Total relief of severe left ventricular outflow obstruction after spontaneous rupture of chordae tendineae in a patient with hypertrophic cardiomyopathy

A Gu Araujo, W V Azeredo, E Arteaga, C Mody

In hypertrophic cardiomyopathy (HCM), rupture of mitral chordae tendineae is infrequent and causes acute haemodynamic deterioration. A 38 year old male patient had chordae rupture leading to prolapse of both mitral leaflets and severe regurgitation, without change in symptomatic status. One year before, he had had mild mitral regurgitation and a resting left ventricle outflow tract of 105 mm Hg that disappeared in the present evaluation. In this unique case, worsening of mitral regurgitation was counterbalanced by total relief of the severe obstruction. This case report highlights the role of the mitral valve apparatus in the genesis of obstruction in HCM, further stimulating surgical techniques in which mitral repair can be the main procedure.

(Heart 2005;91:e35) www.heartjnl.com/cgi/content/full/91/5/e35
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Heart 2005 91: 601-605
doi: 10.1136/hrt.2003.030338

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