Cardiac resynchronization in severe heart failure and left bundle branch block: a single centre experience

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Summary

Objective: To assess the feasibility and long-term outcome of cardiac resynchronization therapy (CRT) in patients with impaired left ventricular function (LVEF <35%), left bundle branch block (QRS ≥130 ms) and dyspnoea NYHA ≥ III at a single centre.

Methods and Results: Forty-seven patients were referred for implantation of a CRT device. In only 4 patients (9%) the device could not be implanted due to technical problems during the procedure. In the remaining 43 patients (65 ± 10 years; 7 female) a CRT device was implanted. Follow-up time was 12 ± 10 months. Twenty-one patients had dilated cardiomyopathy (DCM) and 22 patients had coronary artery disease (CAD). NYHA functional class improved from 3.0 ± 1.4 to 2.5 ± 0.7 (p <0.0001), accompanied by an improvement of LVEF [median 20% (range 15–25) vs 32% (range 20–40); p <0.0001]. A significant reduction of hospitalisation time for heart failure was found when the year before and the year after device implantation [18 days (range 5–27) vs 1 day (range 0–3); p <0.0001] were compared. Twelve (28%) patients, 9 with CAD, and 3 with DCM died. Two CAD patients and all patients with DCM who died had a combined CRT device with implantable cardioverter/defibrillator.

Conclusion: In patients with severely impaired LVEF and wide QRS due to LBBB, CRT is feasible and safe. It improved dyspnoea and LVEF and reduced hospitalisation stays for heart failure during long-term follow-up.

Introduction

Recently, several randomized controlled trials in patients with severe heart failure, reduced left ventricular ejection fraction, and QRS duration ≥130 ms (mainly left bundle branch block) have demonstrated the feasibility and clinical benefit from cardiac resynchronization therapy (CRT) [1–4]. In contrast to the convincing evidence of a 30–40% relative mortality reduction seen in implantable cardioverter/defibrillator (ICD) trials [5, 6] in patients with coronary artery disease with severely impaired left ventricular ejection fraction (LVEF), only one unpublished trial (COMPANION) demonstrated a mortality reduction in CRT compared to optimal medical management [7, 8]. However, meta-analysis from earlier trials of cardiac resynchronization therapy demonstrated a 51% relative mortality reduction for CRT compared to optimal medical therapy alone [9]. Since most of the large CRT trials were performed in highly selected patients referred to selected centres, it remains unclear whether the beneficial outcome observed in these trials is comparable in daily practice. Therefore, the aim of the present observational follow-up study was to assess feasibility and safety of CRT, and to evaluate early and late outcome in a single centre setting.

Methods

Patients

Over a period of 12 ± 10 months a total of 47 patients (40 male, 7 female) received a CRT-system in our hospital for symptomatic (NYHA III/IV) ischemic or non-ischemic heart failure. All patients had left bundle branch block (QRS ≥130 ms) on the surface ECG and a well-established medical therapy for heart failure. No other definite exclusion criteria for CRT were pre-defined.
Implantation of the devices and pre-discharge management

After adequate local anaesthesia, a ventricular electrode was implanted via the cephalic or subclavian vein into the apex of the right ventricle for right ventricular pacing or if needed, also for defibrillation. The electrode for left ventricular pacing was introduced over a guide wire into the coronary sinus and placed into a left ventricular vein, with the largest left ventricular depolarization delay in relation to the right ventricular [10]. Then, a right atrial electrode for right atrial sensing and pacing was implanted. Finally, the CRT device was connected with the electrodes and implanted subcutaneously, or if necessary in a subpectoral position (figure 1). After implantation of the device, optimal CRT was assessed through adjustment of atrioventricular and left ventricular delay to achieve the shortest possible QRS duration on the surface ECG (figure 2 A/B). After implantation, the programming was optimized by Doppler echocardiography (see study limitation). Here, the left ventricle was pre-excited as much as possible without compromising atrial filling of the left ventricle assessed by Doppler echocardiography and of the optimal reduction of left ventricular depolarization delay using continuous Doppler echocardiography between right and left ventricular outflow tract.

Follow-up

Follow-up data on vital status, device integrity, clinical signs of heart failure, necessity of hospitalisation due to heart failure, and echocardiographic assessment of left ventricular ejection fraction was assessed regularly at 3-month intervals.

Statistics

Continuous data are expressed as mean value ± SD or median values with interquartile ranges, where appropriate. The chi-square test was used to compare nominal data. Unpaired Student’s-t-test was used to compare normally distributed continuous data and Mann Whitney or Wilcoxon statistics in case of non-normally data. Survival curves were obtained according to the method of Kaplan-Meier and stratified for patients with CAD and DCM. Two-sided p values ± 0.05 were considered to be statistically significant. Statistical calculations were performed using the statistical package StatView, version 5.0 (SAS Institute Inc., Cary, North Carolina).

Figure 1
X-ray of a patient with CRT device. “A” denotes atrial, “R” right ventricular, and “L” left ventricular electrode.

Figure 2
A: Twelve-lead electrocardiogram of a patient with dyspnoea NYHA class IV and 20% left ventricular ejection fraction due to non-ischemic cardiomyopathy. The intrinsic heart rate shows broad QRS (226 ms) with a left bundle branch block and an AV block I (192 ms).
Figure 2
B: Twelve-lead electrocardiogram of the same patient after cardiac resynchronization showing a smaller QRS (180 ms) and short AV delay (170 ms) with biventricular pacing.

Results

Baseline clinical characteristics, medication, and the number of patients with combined CRT device and ICD (CRT-ICD) are presented in the Table.

Forty-seven patients were referred for implantation of a CRT device within a four-year period. Fluoroscopy time for implantation of the devices was 41 (IQR 23.5–64.3) minutes. Four patients had to be excluded from follow-up investigations. In one patient the CRT device could not be implanted due to technical problems during cannulation of the coronary sinus. In three patients an adequate pacing site of the left ventricle could not be found during implantation (n = 1) or left ventricular capture failure developed shortly after implantation (n = 2). Thus, follow-up investigations were performed in 43 patients with a mean time of 12 ± 10 months.

The programmed mode of the device was DDD in 27, VDD in 9 and VVI in 7 patients. Mean age of study patients was 65 ± 10 years. Twenty-one patients (5 female) were referred for nonischemic dilated cardiomyopathy (DCM) and 22 patients (2 female) for coronary artery disease (CAD). In 11 CAD patients and 13 DCM patients (55.8% of all patients) a CRT-ICD device was implanted. Atrial fibrillation was present in 7 patients (16%), sinus rhythm in 36 patients. Dyspnea NYHA class was 3.0 ± 1.4 at study entry and improved to 2.5 ± 0.7 (p < 0.0001) after implantation of the CRT device, accompanied by a significant improvement of the left ventricular ejection fraction [20% (range 15–25) vs 32% (range 20–40); p < 0.0001]. In addition, a marked narrowing of the QRS complex [172 ms (158–196) vs 148 ms (138–160); p = 0.003] could be observed with CRT. These findings were accompanied by a significant reduction of hospitalisation time for heart failure, when the year before and the year after implantation of the CRT device [18 days (range 4.8–27.3) vs 1 day (range 0–3); p < 0.0001] were compared.

Two patients were referred for heart transplantation during follow-up due to persistent heart failure symptoms with clinical deterioration, one of them died shortly after transplantation. The ICD terminated potentially life-threatening ventricular arrhythmias in 6/13 DCM patients (46%) whereas in only 3/11 CAD patients (27%) sustained ventricular arrhythmias were successfully treated by the device.

Twelve patients (28%) died during follow up, 9 patients with CAD, and 3 patients with DCM (figures 3/4). Five CAD patients died due to sudden cardiac death, 4 due to heart failure. One DCM patient died due to heart failure, one due

<table>
<thead>
<tr>
<th>Age year ± SD</th>
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<tr>
<td>Sex female/male</td>
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<tr>
<td>BMI (SD)</td>
<td>26 (3.2)</td>
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<tr>
<td>QRS ms (IQR)</td>
<td>172 (158–196)</td>
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<tr>
<td>LVEF % (IQR)</td>
<td>20 (15–25)</td>
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<td>NYHA class</td>
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<td>ICD-CRT n (%)</td>
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<td>CRT n (%)</td>
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<td>Diuretics n (%)</td>
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<td>Oral anticoagulation n (%)</td>
<td>32 (75)</td>
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Table 1
Baseline clinical characteristics of the 43 study patients. Data are given in numbers and percentages, mean ± standard deviation, or median values with interquartile ranges where appropriate. Abbreviations: BMI = body mass index; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ICD-CRT = biventricular pacing and implantable cardioverter/defibrillator device; CRT = biventricular pacing device; SD = standard deviation; IQR = interquartile range.
to sudden cardiac death and one after heart surgery. A CRT-ICD device was implanted in only 2 of the nine CAD patients who died whereas all DCM patients had a combined device.

**Discussion**

Data from our prospectively conducted registry have shown the following important findings. Implantation of a CRT device is feasible in about 90% of all patients referred for CRT. Biventricular pacing leads to a significant reduction in dyspnoea of about 0.5–1 NYHA classes in patients with DCM and CAD, and improves left ventricular ejection fraction. However, CRT does not stop natural history of the disease as mortality rate over a relatively short follow-up (12 months) is high (25.6%). Most patients died of sudden cardiac death, which questions the role of CRT pacemakers without defibrillator backup. Our findings of improved outcome in functional NYHA class and LVEF are in line with two published single centre experiences of CRT over a follow-up period of 6 and 12 months, respectively [11, 12]. In addition, several controlled clinical trials have shown recently, that CRT restores the synchronous contraction of both cardiac ventricles and improves clinical endpoints such as quality of life, 6-minute walk test, oxygen uptake, and left ventricular ejection fraction [2–4]. However, in none of these trials a mortality benefit or a reduction of hospitalisation time could be demonstrated in favour of cardiac resynchronization therapy. Therefore, CRT until now should only be recommended for patients with severely impaired LVEF (<35%) and left bundle branch block (>130 ms) in whom quality of life did not improve and dyspnoea NYHA III/IV persists despite optimal medical therapy. Unpublished data from the COMPANION trial [8] have a significant combined all-cause mortality reduction as well as a reduction of all-cause hospitalisation time in CRT patients, compared to optimal medical therapy alone. Included were 1634 patients with NYHA class III or IV heart failure, sinus rhythm, QRS ≥120 ms, LVEF ≤35%, and left ventricular end-diastolic dimension ≥60 mm.

Biventricular pacing compared to optimal medical therapy led to a 35.8% (p <0.001) reduction of the combined endpoints “all-cause mortality” and “heart failure hospitalisations” therapy but no significant (23.9%, p = 0.12) reduction in “all cause mortality”. Patients with CRT-ICD devices had a larger, 39.5% (p <0.001) reduction of the combined endpoints “all-cause mortality” and “heart failure hospitalisations”, and a 43.4% (p = 0.002) reduction in all-cause mortality compared to medical therapy [8].

Discussing the present data with respect to the literature, we have learned over the last years that patients with CAD referred for CRT due to symptomatic and severely impaired LVEF should in addition to the CRT device receive an ICD [5, 6]. The high mortality rate in our CAD patients without implanted ICD dramatically supports the published data. In DCM patients with severely impaired LVEF no mortality benefit has yet been demonstrated for an ICD implantation compared to medical therapy with amiodarone alone [13, 14]. Therefore, ICD implantation for DCM is not recommended with regard to different clinical trials performed over the last years [15, 16]. Nevertheless, a high proportion of our DCM patients received an ICD due to either inducible ventricular tachycardias during programmed ventricular stimulation or to patient/investigators choice. Over a median follow-up time of only 12 months, in 46% of these patients at least one life-threatening ventricular tachycardia could be successfully terminated by the ICD. However, this finding should not be overestimated since there...
was no control group to investigate a potential survival benefit of the ICD. Interestingly, our data are supported by other investigators [17] who also found that appropriate shocks for ventricular tachycardia or ventricular fibrillation are a common finding in 37% of DCM patients. ICDs may therefore play a role in the prevention of sudden cardiac death in selected DCM patients and further prospectively conducted studies are warranted to definitely clear this point.

Implantation of ICDs and CRT devices are expensive. Mean costs of a CRT device are about 20,000 SFr. Costs for an integrated CRT-ICD are about 60,000 SFr. In addition, longevity of the device lies between 5 and 10 years. Given the high number of about 5% of the general population over 65 years suffering from heart failure [18, 19] and the fact that at least 7–14% of patients qualify for such devices [20], this would have a relevant impact on health costs over the next decade.

In accordance with unpublished data from the COMPANION trial [8] our own findings have shown an impressive reduction in hospitalisation time for heart failure accompanied by a significant improvement in dyspnoea and quality of life. In addition, our data and findings from other investigators have demonstrated that implantation of a CRT device is safe, that long-term pacing in the coronary sinus has no clinical adverse effects [21] and that the implantation of the devices is feasible in more than 90% of the patients routinely admitted due to severe heart failure with an acceptable median fluoroscopy time of 41 minutes.

Study limitation

Today, echocardiographic assessment of the AV time, measurement of the interventricular- (mechanical delay between left and right ventricular outflow tract) and intraventricular- (delay between the anterior and posterior wall of the left ventricle in the short axis view of the left ventricle) delay of the left ventricle are standard parameters for optimizing CRT. Our registry of CRT patients started at the end of 1999. Therefore, these parameters were not routinely assessed in all patients from 1999 to 2001 and echocardiographic assessment was sometimes performed visually only.

However, after the studies from Auricchio [22] and Pitzalis [23] in 2002 Doppler echocardiographical optimizing of the AV time, and measurement of inter- and intraventricular delay became a standard procedure in our CRT patients. Analysing this subgroup of patients, the optimal AV delay was 112 ± 18 ms. Focusing on the optimized AV delay, CTR reduced the interventricular delay from 48 ± 19 ms to 21 ± 22 ms; p <0.0001, and the intraventricular delay from 181 ± 106 to 120 ± 83; p = 0.002. However (maybe due to the small number of patients), we found no significant correlation between QRS duration and inter- or intraventricular delay of the left ventricle.

Conclusion

Over the last years CRT has become an important and promising new method for the treatment of heart failure patients with significant cardiac dyssynchrony of the left ventricle due to left-bundle-branch block. To date, despite optimal medical therapy all patients with dyspnoea NYHA III/IV due to coronary disease or dilated cardiomyopathy should be evaluated for CRT. However, some of these patients (20–30%) do not improve heart failure symptoms after implantation of a CRT device. Although much effort has been undertaken to predict responders prior to implantation of a CRT device over the last years, we have no easily applicable method to identify the responders up to now. The most promising approach to identify CRT responders today is: 1) to assess viability of the left ventricular free wall, and 2) to measure interventricular delay, which should be ≥40 ms echocardiographically. To individually optimize programming of the AV-interval after implantation of the CRT device is mandatory.

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