Very long term follow-up of cardiac resynchronization therapy: Clinical outcome and predictors of mortality

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Abstract

Background: Cardiac resynchronization therapy (CRT) improves symptoms, left ventricular ejection fraction (LVEF) and survival in patients with heart failure and wide QRS, however, long term clinical outcome is unknown.

Aims: To identify predictors of mortality and evaluate the effects of CRT after long term follow-up.

Methods: Consecutive patients treated with CRT between 1997 and 2002 were included. We collected clinical information from patient files. Patients who were still alive underwent echocardiography and clinical evaluation.

Results: We included 179 patients (median age 65.5 years, 144 male). Median follow-up for survival was 4.0 years. Mortality at one and five years was 15% and 53%, respectively. Predictors of mortality were, ischaemic heart disease (IHD), higher NYHA class and lower LVEF (<22.5%) at baseline, and no improvement in NYHA class at early follow-up. NYHA class remained stable from early to long term follow-up after a median of 5.1 years. In patients with non-IHD median LVEF increased significantly from early to long term follow-up (39% vs. 50% p=0.007).

Conclusion: Predictors of mortality in patients with CRT are IHD, lower LVEF and higher NYHA class at baseline, and no symptomatic response to CRT. After 5 years follow-up, clinical effects are sustained, and in patients with non-IHD further improvements in LVEF are observed.

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Keywords: Heart failure; Cardiac resynchronization therapy; Mortality; Predictors

1. Introduction

Cardiac resynchronization therapy (CRT) is a well established therapy for patients with heart failure, low left ventricular ejection fraction (LVEF), and prolonged QRS duration [1]. Randomised controlled trials have shown that CRT improves symptoms of heart failure, quality of life, exercise capacity, and LVEF [2–4]. However, most of these studies have a short follow-up period of between 6 months and one year. Whether these benefits are sustained over the long term is not well documented. In recent studies CRT with or without defibrillator (CRT-D and CRT) has also been shown to reduce all cause mortality [5,6]. The primary aim of the present study was to identify predictors of long term mortality in consecutive patients treated with CRT. Furthermore, we aimed to investigate the long term effects of CRT on clinical status and echocardiographic parameters in patients with ischaemic heart disease (IHD) and non-ischaemic heart disease (non-IHD).

2. Methods

2.1. Patients

To evaluate the very long term effect, defined as >4 years, of CRT or CRT-D we included consecutive patients treated at Aarhus University Hospital, Skejby from January 1, 1997 to...
December 31, 2002. Patients undergoing upgrade of conventional devices to CRT in the period were also included. Survival data were obtained for the entire cohort and causes of death were collected from the National Death Registry. Patients still alive at October 1, 2006 were asked to participate in the re-evaluation of echocardiographic and clinical status. The study was approved by the Regional Ethics Committee and The Danish Data Protection Agency. The investigation conforms with the principles outlined in the Declaration of Helsinki. All subjects undergoing extended follow-up evaluation gave written informed consent to participate in the study.

2.2. Implantation

After cannulation of the coronary sinus and obtaining a venogram left ventricular (LV) leads were positioned preferably in a lateral or posterolateral tributary to the coronary sinus [7]. Various transvenous delivery systems, LV leads, and CRT devices with or without ICD from different companies were used. In the period from 1997 to 1999 left ventricular pacing was achieved by placing a Slimline® lead (Vitatron) in the coronary sinus transvenously using a coronary Amplatz catheter. One patient received a left ventricular epicardial lead via thoracotomy early in the study period.

2.3. Clinical data

We collected clinical information from the entire patient group retrospectively including the New York Heart Association (NYHA) classification, heart failure etiology, QRS duration, and echocardiography before (baseline) and at the first visit after (early follow-up (FU)) the pacemaker implantation, documented in patient files as a part of routine clinical care.

At long term FU all patients were classified according to NYHA classes and medical history was recorded. A standard 12 lead electrocardiogram was recorded at a speed of 25 mm/s and QRS duration was measured manually with CRT-on and CRT-off. QRS duration was defined as the widest QRS in any of the 12 standard leads. Echocardiography was performed with the patient in the left lateral decubitus position using a commercially available system (Vingmed System FiVe, GE-Vingmed Ultrasound AS, Horten, Norway). Left ventricular ejection fraction (LVEF) was measured using visual assessment by an experienced observer [8], and left ventricular end diastolic diameter (LVEDD) was measured using M-mode [9].

2.4. Statistics

Normally distributed data are presented as mean±SD, otherwise as median and 25th to 75th percentiles. Absolute frequency and percentages are reported for categorical data. The difference between groups was evaluated with t-tests for Gaussian variables, and Wilcoxon rank-sum tests for non-Gaussian variables. Pearson’s chi-squared test was used for all categorical data. Univariate Cox regression analysis was used for the analyses of predictors of mortality. All variables exhibiting a p-value <0.1 in univariate analysis were entered into the multivariate Cox regression analysis. Variables considered for multivariate analysis were age, sex, diabetes, atrial fibrillation, implantable cardiac defibrillator, NYHA class, LVEF and QRS duration at baseline. For LVEF and QRS duration at baseline, median values were used to dichotomize continuous variables. Improvement in NYHA class at early FU and a reduction in QRS duration after implantation were also considered for multivariate analysis. Hazard ratios (HR) with 95% confidence intervals (CI) are reported. Mortality rate was summarized by construction of Kaplan–Meier curves. All patients that underwent heart transplantation were censored at the date of the operation. All p-values are two-sided and nominal. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using STATA software (STATA for Windows, version 10.0).

3. Results

3.1. Patients

One hundred and seventy nine patients received CRT or CRT-D in the study period. Of these, 76 patients were alive on October 1, 2006, 90 patients had died, 12 patients had undergone heart transplantation and one had moved abroad. Of the 76 patients alive, six patients did not participate in the long term FU examination, three patients were not physically able and three patients refused. The median age at implantation was 65.5 (57–70) years, the median follow-up time for survival was 4.0 (1.5–5.0) years, the median time from implantation to early follow-up was 0.7 (0.2–1.6) years, and the median time from implantation to long term FU was 5.1 (4.4–6.1) years. In 57 patients we obtained LVEF at baseline, early FU, and long term FU and in 53 patients we obtained LVEDD at both baseline and long term FU. There were 144 men, 86 (60%) with IHD and 58 (40%) with non-IHD, and 35 women, 13 (37%) with IHD and 22 (63%) with non-IHD. In patients participating in the long term follow-up, the proportion of patients receiving beta blockers increased from 55% to 83%, ACE-inhibitors changed from 87% to 80%, loop diuretics decreased from 88% to 63% and aldosterone antagonists changed from 57% to 63% from baseline to long term follow-up. Baseline data for all patients and for the group of patients participating in long term FU, including clinical parameters, pharmacological therapy, QRS duration and echocardiographic measurements are shown in Table 1.

3.2. Predictors of mortality

The cumulative mortality was 15 (95% CI 11 to 21)% at two years, 28 (95% CI 22 to 35)% and 53 (95% CI 45 to 61)% at one, two and five years, respectively (Fig. 1). Causes of death included heart failure (HF) in 40 (44%) patients, sudden cardiac death (SCD) in 21 (23%) patients, acute myocardial infarction in 7 (8%) patients, non-cardiac related deaths in 15 (17%) patients, and unknown in 7 (8%) patients. There were no differences in
cause of death between patients with CRT and CRT-D, including HF in 11 (46%) vs. 29 (44%) patients, SCD in 6 (25%) vs. 15 (23%) patients, acute myocardial infarction in 2 (8%) vs. 5 (8%) patients, non-cardiac related deaths in 4 (17%) vs. 11 (17%) patients, and unknown in 1 (4%) vs. 6 (9%) patients. There was no difference in median time to SCD and death from HF or heart transplantation: 1.7 (0.8 – 3.8) years vs. 1.3 (0.3 – 2.6) years, respectively \( p = 0.245 \). Predictors of mortality are listed in Table 2. Significant baseline univariate predictors of mortality were older age, male sex, higher NYHA class, IHD, and lower LVEF (<22.5%). Also no improvement in NYHA class at early FU and no QRS shortening after implantation were associated with higher mortality in univariate analysis. In multivariate analysis older age (HR 1.05 95% CI 1.02 to 1.08) per year, NYHA class IV and III compared to NYHA class II (HR 6.5 95% CI 1.89 to 22.36 and HR 3.13 95% CI 1.09 to 9.01, respectively), NYHA class IV compared to NYHA class III (HR 2.07 95% CI 1.05 – 4.10), LVEF (<22.5%) (HR 1.71 95% CI 1.02 to 2.89) and IHD (HR 2.03 95% CI 1.15 to 3.76), as well as no improvement in NYHA class at early FU (HR 3.02 95% CI 1.70 to 5.38) were significant predictors of mortality. In international guidelines, CRT is only indicated in patients with NYHA III and IV. If we excluded patients with NYHA class I and II from the analysis the same variables were significant predictors of mortality.

3.3. Long term follow-up

3.3.1. NYHA class

The long term follow-up included 70 patients who were alive on October 1, 2006. In five patients information on NYHA functional class was missing at baseline or at early follow-up. The NYHA functional class improved from 0/14/41/10 (NYHA I/II/III/IV) at baseline to 15/36/14/0 at early FU and 12/27/25/1 at long term FU. Baseline NYHA class differed significantly from both early FU and long term FU \( (p<0.001) \). There was no difference between NYHA classes at early and long term FU \( (p=0.17) \). Patients with IHD and non-IHD both improved in NYHA functional class at early FU \( (p<0.001 \) and \( p<0.001 \), respectively) and long term FU \( (p<0.001 \) and \( p=0.033 \), respectively) compared to baseline. Furthermore we found no significant difference in NYHA class between early and long term FU in patients with IHD or non-IHD \( (p=0.39 \) and 0.15, respectively).

3.3.2. QRS duration

The mean paced QRS duration immediately after implantation and at long term FU was 146 ms (±30) and 132 ms (±34) respectively \( p = 0.013 \). Forty-nine patients had intrinsic rhythm at long term follow-up. This group of patients had a baseline mean intrinsic QRS duration of 174.0 ms (±34) and a long term FU intrinsic QRS (CRT-off) of 150 ms (±31) \( (p<0.001) \) (Fig. 2).

3.3.3. Echocardiography

The median LVEF increased from 25 (20–25)% at baseline to 35 (25–53)% at long term FU \( (p<0.001) \). In a subgroup of 57 patients we also obtained echocardiographic data from early FU and found a statistically significant further
increase in median LVEF from early FU to long term FU 30 (25–45)% vs. 38 (25–58)% \((p=0.016)\).

In patients with IHD, median LVEF increased from 22.5 (17.5–25)% at baseline to 28 (20–45)% at early FU \((p=0.005)\), and did not change significantly from early to long term FU 25 (20–43)% \((p=0.701)\). In non-IHD patients LVEF increased significantly from 25 (17.5–27.5)% at baseline to 39 (25–48)% at early FU \((p<0.001)\), and increased further to 50 (30–60)% at long term FU \((p=0.007)\). We found a significant decrease in LVEDD from median 67 (62–74) mm to 63 (50–70) mm \((p<0.001)\), in the 53 patients where we obtained data both at baseline and at long term FU. There was no difference in LVEDD from baseline to long term FU in patients with IHD-median 69 (63; 73) mm vs. 67 (64–72) mm \((p=0.39)\). We found a statistically significant reduction in median LVEDD in non-IHD patients from 66 (62–75) mm to 56 (47–68) mm \((p<0.001)\) from baseline to long term FU.

Table 2
Predictors of mortality in patients with CRT

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate HR</th>
<th>95% CI</th>
<th>(p)</th>
<th>Multivariate HR</th>
<th>95% CI</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age (per year)</td>
<td>1.05</td>
<td>(1.02–1.07)</td>
<td>0.000</td>
<td>1.05</td>
<td>(1.02–1.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>2.00</td>
<td>(1.04–3.68)</td>
<td>0.037</td>
<td>1.61</td>
<td>(0.74–3.50)</td>
<td>0.231</td>
</tr>
<tr>
<td>IHD</td>
<td>2.11</td>
<td>(1.35–3.30)</td>
<td>0.001</td>
<td>2.03</td>
<td>(1.15–3.76)</td>
<td>0.014</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.94</td>
<td>(0.54–1.63)</td>
<td>0.822</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.92</td>
<td>(0.59–1.40)</td>
<td>0.709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>1.05</td>
<td>(0.65–1.67)</td>
<td>0.852</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA II</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA III</td>
<td>2.97</td>
<td>(1.19–7.4)</td>
<td>0.019</td>
<td>3.13</td>
<td>(1.09–9.01)</td>
<td>0.034</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>4.575</td>
<td>(1.73–12.08)</td>
<td>0.002</td>
<td>6.5</td>
<td>(1.89–22.36)</td>
<td>0.003</td>
</tr>
<tr>
<td>NYHA VI vs. III</td>
<td>1.53</td>
<td>(0.94–2.51)</td>
<td>0.085</td>
<td>2.07</td>
<td>(1.05–4.10)</td>
<td>0.037</td>
</tr>
<tr>
<td>LVEF baseline (&lt;22.5)</td>
<td>2.07</td>
<td>(1.30–3.18)</td>
<td>0.001</td>
<td>1.71</td>
<td>(1.02–2.89)</td>
<td>0.042</td>
</tr>
<tr>
<td>QRS baseline (&gt;172 ms)</td>
<td>1.11</td>
<td>(0.66–1.88)</td>
<td>0.683</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate HR</th>
<th>95% CI</th>
<th>(p)</th>
<th>Multivariate HR</th>
<th>95% CI</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No improvement in NYHA class</td>
<td>1.89</td>
<td>(1.18–3.04)</td>
<td>0.008</td>
<td>3.02</td>
<td>(1.71–5.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No QRS shortening</td>
<td>1.79</td>
<td>(1.15–2.77)</td>
<td>0.012</td>
<td>1.62</td>
<td>(0.95–2.77)</td>
<td>0.074</td>
</tr>
</tbody>
</table>

Reported as hazard ratio (HR) with 95% confidence interval (CI).

4. Discussion

The present study is the first to evaluate very long term clinical outcome and predictors of mortality in a larger cohort of patients treated with CRT.

4.1. Patients

More patients with severe symptomatic heart failure (NYHA IV) \([10,11]\) were included in our study group and the median LVEF was low as compared with prior studies \([5,6,10,11]\). CRT is indicated for patients with heart failure, NYHA class III and IV, reduced LVEF and broad QRS. As a
prophylactic measure CRT devices were also implanted in a small group of primarily younger patients in NYHA class II. We also included patients with atrial fibrillation and previous devices, which were excluded from most clinical trials in this period. Other baseline characteristic such as age, sex, QRS duration and LVEDD were similar to that observed in other comparable studies. During the study period, beta blockers were shown to reduce mortality in patients with chronic heart failure, and as a result the proportion of the surviving patients receiving beta blockers increased from baseline to long term follow-up.

4.2. Predictors of mortality

All cause one year mortality (15%) was higher than reported in other studies [5,10–12]. However, in studies with a comparable proportion of patients with IHD, the one year mortality was similar to our study [6,13]. The 1 and 5 year mortality in this study does not differ from the mortality rate for all CRT patients treated in Denmark from 1996 to 2006 [14].

Higher NYHA class prior to implantation was a strong predictor of mortality in this study, as has been reported previously [10,15,16].

No improvement in NYHA class at early follow-up was also a strong predictor of mortality. This confirms that a symptomatic response to treatment is associated with improved long term survival and is consistent with the studies of Cha et al. and Molhoek et al. [13,16]. The effect of heart failure aetiology on mortality in patients with CRT is controversial. Some studies have found no difference in mortality between patients with IHD and non-IHD [10,17,18]. One study has demonstrated that non-IHD patients seem to have a better prognosis [11]. Our mortality analysis confirms a better outcome of CRT in patients with non-ischaemic heart failure aetiology.

Lower LVEF (<22.5%) at baseline was also related to mortality in this study and these findings are supported by a larger multicenter prospective study [10].

We found no relation between mortality and QRS duration before implantation which is in line with earlier observations [19]. However, in this early study of CRT, more than 85% of patients had a QRS duration over 150 ms.

Other variables which have been shown to be related to survival in previous studies are: an absolute change in LVEF of at least 5% [20] and a relative change in left ventricular end systolic dimension of at least 10% [21]. However, changes in left ventricular dimensions or ejection fraction were not considered for our survival analysis, because of the risk of weakening the statistical power of the analysis.

Mortality in heart failure patients without CRT is predicted by several factors including ischaemic aetiology, lower LVEF and higher NYHA class. This study confirms these findings also in patients with heart failure who are treated with CRT.

4.3. Clinical characteristics of long term survivors

Most previous studies evaluating the effect of CRT on symptoms and left ventricular function have a relatively short follow-up period [2–4]. Few studies have extended their follow-up period to 2 or 3 years. To our knowledge, this is the first study to extend the FU period to 5 years (median).

Our study shows that the benefits of CRT on symptoms are sustained in long term survivors. A similar effect was observed in two prospective studies with a mean follow-up of 2 and 3 years [16,22].

We observed that the beneficial changes in LVEF measured shortly after CRT are preserved after long term FU. An interesting observation is that patients with non-IHD show a further increase in LVEF from early to long term FU, while there was no further improvement in IHD patients. This trend was also demonstrated in another prospective study with 2 years follow-up [20]. A large proportion of patients with non-IHD showed an improvement in LVEF to >50%. This observation was also found in another study and these patients have been described as hyper-responders [23]. Two large prospective studies present similar long term findings for NYHA class and LVEF as our study, but after a mean follow-up time of approximately 2 and 3 years [11,24].

We observed long term reverse remodelling with a decrease in LVEDD only in non-IHD patients. To our knowledge only one other study has previously reported a long term effect on LVEDD [11].

Some studies have demonstrated a decrease in intrinsic QRS duration after 3–14 months CRT [25,26]. This electrical remodelling was confirmed in our study after a median of 5.1 years CRT. In contrast, a recent study found a trend towards prolongation of intrinsic conduction at long term follow-up [27]. The mechanism behind any electrical remodelling is unclear. It has been suggested that it may be due to regeneration in conduction tissue or in intramyocardial connections as a result of mechanical remodelling or improved haemodynamics combined with a diminishing distance for electrical conduction due to a decrease in left ventricular volume.

This study presents the typical limitations of similar retrospective studies. The patients are more heterogeneous, there were different clinical and echocardiographic observers during the study period, and there was no blinding or control group. Furthermore, our study did not include other parameters usually considered of interest in modern CRT, especially intraventricular dyssynchrony. The number of events in this study was not sufficient to perform subgroup analyses with respect to gender or mode of death. We also lacked echocardiographic measurements and symptomatic evaluation at early FU in a minority of the patients. However, the study presents data on a large cohort of consecutive patients treated in a large volume centre and more than 90% of long term survivors underwent clinical evaluation after 5 years of FU.

In conclusion, in a real life setting one and five year mortality for CRT is 15% and 53%. Predictors of mortality are higher NYHA class at baseline, no improvement in NYHA...
class at early FU, ischaemic heart disease, and lower LVEF at implantation. These predictors do not differ from a general population of patients with congestive heart failure without CRT.

In long term survivors (median FU 5.1 years) the early symptomatic and echocardiographic effects of CRT are sustained. Furthermore the non-IHD subgroup displayed a significant improvement in LVEF from early to long term FU, and showed long term reverse remodelling with a decrease in LVEDD.

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References