Chapter 19

Effect of cardiac resynchronization therapy in patients with New York Heart Association functional class IV heart failure

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Am J Cardiol 2010;106(8):1146-51

ABSTRACT

Background: Cardiac Resynchronization Therapy (CRT) is considered a class I indication in treatment of New York Heart Association (NYHA) functional class III and IV heart failure patients. However, only a small number of patients in the large clinical trials were in NYHA functional class IV. Therefore, little is known about the effects of CRT in this group. Consequently, we evaluated the effects of CRT in NYHA functional class IV heart failure patients.

Methods: Of all patients referred for CRT implantation, 61 patients with symptoms according to NYHA functional class IV were included. All patients were evaluated before implantation and at 6 months follow-up for clinical changes according to the Clinical Composite Score (CCS) and changes in left ventricular (LV) volumes and function. Additionally, survival was evaluated during long-term follow-up.

Results: At 6 months follow up, 9 (15%) patients had died and 2 (3%) patients were admitted for worsening heart failure. The remaining 39 (64%) patients improved according to the CCS. Reductions in both LV end-systolic volume (from 167±88 ml to 147±93 ml, $p = 0.009$) and LV end-diastolic volume (from 211±100 ml to 199±113 ml, $p = 0.135$) were observed, as well as a significant improvement in LV ejection fraction (from 22±8% to 28±9%, $p<0.001$). During a mean follow-up of 30±26 months, 36 patients (59%) died, 27 (75%) of which due to worsening heart failure. Respective 1- and 2-year mortality rates were 25% and 38%.

Conclusions: CRT reduces LV volumes and improves cardiac function in patients with NYHA functional class IV heart failure. Nevertheless, (heart failure) mortality remains high in these patients.

INTRODUCTION

Heart failure is a growing health-care problem in the western world. It is estimated that approximately 5 million people in the United States suffer from heart failure and heart failure hospitalizations have increased drastically over the last 20 years.[1] Cardiac resynchronization therapy (CRT) has emerged as a new treatment option for patients with drug-refractory end-stage heart failure. Several large trials have demonstrated that CRT not only results in improvement in left ventricular (LV) function, heart failure symptoms and quality of life (QoL), but also in a reduction in heart failure hospitalizations and mortality in patients with severe symptomatic heart failure. Accordingly, current guidelines consider CRT as a class I indication for patients in New York Heart Association (NYHA) functional class III-IV, with depressed LV ejection fraction (LVEF) ≤35%, and a wide QRS complex (≥120 ms).[2] However, only a small percentage of patients enrolled in the large multi-center trials constituted of NYHA functional class IV patients.[3, 4] In brief, of 10,803 patients enrolled in these large trials, only 451 patients (4.2%) were in NYHA functional class IV.[5] Therefore little is known about the effects of CRT in this group. It remains yet to be determined whether and to which extent these patients benefit from CRT. The aim of this study was to determine the possible beneficial effects of CRT on LV volumes and function, clinical symptoms and long-term outcome in patients in NYHA functional class IV.

METHODS

Patient population and protocol

Patients were referred for CRT according to the current guidelines: advanced symptoms of heart failure (NYHA functional class III or IV), LV ejection fraction (LVEF) <35%, sinus rhythm and a wide QRS complex (>120 ms).[2] Patients with a recent myocardial infarction or revascularization (≤3 months) were excluded. Of all patients referred for CRT implantation, 61 patients who presented with symptoms according to NYHA functional class IV heart failure were included in the present study. Etiology of heart failure was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in 1 or more of the major coronary arteries) and/or a history of myocardial infarction or prior revascularization. Before and 6 months after CRT implantation, extensive clinical and echocardiographic evaluation was performed.

Clinical evaluation consisted of assessment of heart failure symptoms according to the NYHA classification. Assessment of quality of life was performed using the Minnesota Living

with Heart Failure Questionnaire (high scores indicating poor quality of life)[6] and when possible, exercise capacity was measured using the 6-minute walk test.[7]

Echocardiography

All patients underwent echocardiography in the left lateral decubitus position before and six months after CRT implantation. Imaging was performed using a commercially available echocardiographic system (VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber) views. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cineloop format. A minimum of three consecutive beats were recorded from each view and the images were digitally stored for off-line analysis (EchoPac 108.1.5, General Electric Vingmed Ultrasound, Milwaukee, USA). LV end systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LVEF were measured from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule.[8] Severity of mitral regurgitation was assessed according to current guidelines.[9]

Device implantation

The LV lead was inserted transvenously via the subclavian route. A coronary sinus venogram was obtained using a balloon catheter. Next, the LV pacing lead was inserted through the coronary sinus with the help of an 8Fr guiding catheter and positioned as far as possible in the venous system, preferably in a (postero-) lateral vein. The right atrial and ventricular leads were positioned conventionally. Nine (15%) patients received a CRT device without defibrillator, while 52 (85%) patients received a device with a defibrillator. Devices used were: Contak Renewal, Contak TR or Contak CD, Guidant USA, InSync Marquis, InSync III or InSync Sentry, Medtronic Inc. USA and Lumax 340, Biotronik, Germany.

Clinical follow-up

For assessing clinical changes after CRT, the heart failure clinical composite (CCS) score was used.[10] CCS was classified as follows:

•*Worsened*: the patient died or was hospitalized for or associated with worsening heart failure, demonstrated worsening in NYHA functional class at last observation carried forward, had moderate or marked worsening of patient global assessment score at last observation

carried forward, or permanently discontinued CRT because of or associated with worsening heart failure.

•*Improved*: the patient had not worsened as defined above and demonstrated improvement in NYHA functional class at last observation carried forward or had moderate or marked improvement in patient global assessment score at last observation carried forward.

•*Unchanged*: the patient had neither improved nor worsened.

Other clinical measures included: change in NYHA functional class, change in distance covered in the 6-minute walk test and change in QoL score. Echocardiographic changes after CRT were assessed by comparing LVESV, LVEDV and LVEF at 6-months follow-up with baseline measurements.

During long-term follow-up, survival and heart failure hospitalizations were reported. Primary end-point was all-cause mortality. Secondary end-point was hospitalization for heart failure. Heart failure hospitalization was defined as admission to the hospital for intravenous diuretics and/or inotrope treatment. Outcome data were collected by chart review, device interrogation and telephone contact.

Statistical analysis

Continuous data are presented as mean±SD, and dichotomous data are presented as numbers and percentages. Comparison of data within patients (at baseline and follow-up) was performed by using the paired samples T-test. Survival was investigated with the Kaplan-Meier method. The effect of different variables on the primary end-point was measured by the Cox proportional hazards model. Variables that showed a statistically significant effect in the univariate analyses were entered in the multivariate Cox proportional hazards model. All analyses were performed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). All statistical tests were 2-sided. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics are presented in Table 1. Most patients were male (72%) and the underlying cause of heart failure was ischemic cardiomyopathy in 62%. Patients had severely depressed LV function (mean LVEF 21±7%) with extensive LV dilatation (mean LVEDV 215±93 ml and mean LVESV 171±82 ml). Medication included diuretics in 92%, angiotensin-converting enzyme-inhibitors in 80% and beta-blockers in 59%. None of the patients were on inotropic support at the time of device implantation. A total of 10 (16%) patients were already admitted for heart failure at the time of implantation.

Table 1. Patient characteristics (n = 61)

Age (years)	68 ± 10
Men (n)	44 (72%)
Ischemic heart failure	38 (62%)
Resting heart rate	75 ± 12
Rhythm (n)	
Sinus rhythm	40 (66%)
Atrial fibrillation	16 (26%)
Paced	5 (8%)
QRS duration (ms)	164 ± 26
QRS morphology (n)	
Left bundle branch block	44 (72%)
Right bundle branch block	6 (10%)
Ventricular pacing	11 (18%)
Diabetes mellitus (n)	16 (26%)
eGFR (ml/min/1.73m^2)	53 ± 23
6-minute walk test (m)	127 ± 71
Quality of Life score	54 ± 15
LV end-systolic volume (ml)	171 ± 82
LV end-diastolic volume (ml)	215 ± 93
LV ejection fraction (%)	21 ± 7
Mitral regurgitation (grade)	2.0 ± 1.2
Medication (n)	
Anticoagulants	52 (85%)
Diuretics	56 (92%)
ACE-inhibitors/AII-blocker	49 (80%)
Beta-blockers	36 (59%)
Spironolactone	34 (56%)
Digoxine	17 (28%)

ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate

Clinical changes at 6 months follow-up

At 6 months follow-up, 9 (15%) patients had died (6 patients died of worsening heart failure, 2 patients died suddenly, and 1 patient died due to a malignancy). Furthermore, 2 (3%) patients were admitted for worsening heart failure. Therefore, these 11 (18%) patients were classified as *worsened* according to the CCS. Of the remaining patients, 39 (64%) patients *improved* and 11 (18%) patients were classified as *unchanged* (Figure 1). The QoL score improved from 52.8±13.9 to 38.8±18.8 ($p<0.001$) and the distance covered in the 6 MWT increased from 135±74 m to 258±136 m ($p<0.001$). Finally, NYHA functional class decreased from 4.0±0 to 2.7±0.8 ($p<0.001$).

In addition to clinical changes, a significant reduction in LVESV was observed at 6 months follow-up, from 167±88 ml to 147±93 ml, $p = 0.009$ (Figure 2, panel A). There was a small, but

non-significant reduction in LVEDV, from 211±100 ml at baseline to 199±113 ml at follow-up, p = 0.135 (Figure 2, panel B). Mean LVEF increased from 22±8% at baseline to 28±9% at follow-up, p<0.001 (Figure 2, panel C). Of note, mean QRS duration at 6 months follow-up was 156±26 ms, p = 0.058 vs. baseline.

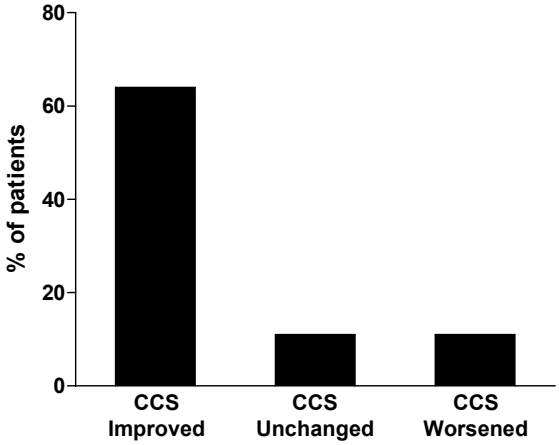

Figure 1. Clinical changes according to the Clinical Composite Score results. At 6 months follow-up, 11 (18%) patients were classified as *worsened,* 39 (64%) patients *improved* and 11 (18%) patients were classified as *unchanged.*

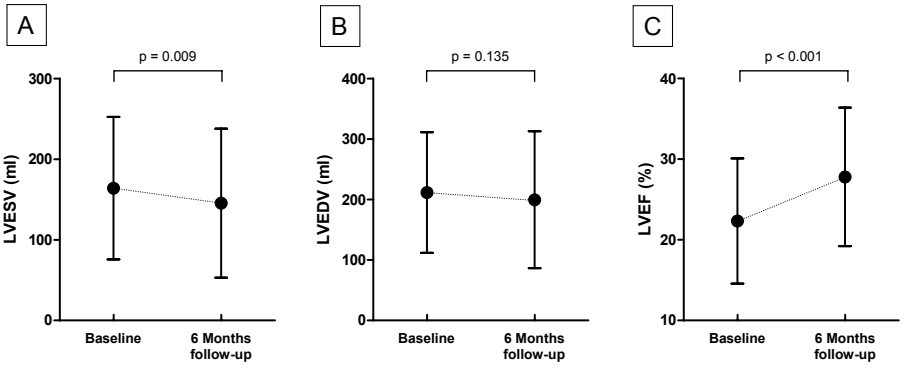

Figure 2. Echocardiographic changes in left ventricular end-systolic volume (LVESV) (Panel A), left ventricular end-diastolic volume (LVEDV) (Panel B) and left ventricular ejection fraction (LVEF) (Panel C) between baseline and 6 months follow-up. A decrease in LVESV (from 167±88 ml to 147±93 ml, p = 0.009) and LVEDV (from 211±100 ml to 199±113 ml, p = 0.135) were observed. In addition, LVEF increased from 22±8% at baseline to 28±9% at follow-up, p<0.001.

Clinical follow-up, long-term results

During a mean long-term follow-up of 30±26 months, 14 (23%) other patients were admitted for heart failure. Of note, 7 patients were admitted once, 1 patient was admitted twice, 3 patients had 3 admissions for heart failure, 1 patient was admitted 4 times, 1 patient was admitted 5 times, and finally, 1 patient had a total of 8 heart failure hospitalizations.

Mean duration of hospitalization in these patients was 26±29 days (Figure 3). In total, 36 (59%) patients died. From these 36 patients, 27 (75%) died due to worsening heart failure. The survival curve for all-cause mortality is displayed in Figure 4. Respective 1- and 2-year mortality rates were 25% and 38%.

Univariate and multivariate Cox proportional hazard analyses were performed for all-cause mortality. Variables that proved to be significantly associated with outcome in the univariate Cox proportional hazards model were the eGFR, the 6 MWT, the QoL score and extent of mitral regurgitation (Table 2). Higher baseline eGFR resulted in superior survival, with a hazard ratio (HR) of 0.97 per ml/min/1.73m^2 increase; 95% confidence interval (CI) 0.95-0.98, p<0.001. More distance covered in the 6 MWT was also associated with better survival, with a HR of 0.99 per m; 95% CI 0.99-1.00, p<0.001. Higher QoL score was associated with worse survival, with a HR of 1.03 per point, 95% CI 1.00-1.05, p = 0.043. Finally, higher extent of mitral regurgitation was associated with worse survival, with a HR of 1.51 per grade, 95% CI 1.16-1.97, p = 0.002. The multivariate Cox proportional hazards model showed that baseline eGFR was the only baseline characteristic that was independently associated with all-cause mortality (Table 2), with a HR of 0.98; 95% CI 0.96-0.99, p = 0.013 per increase of 1 ml/min/1.73m^2.

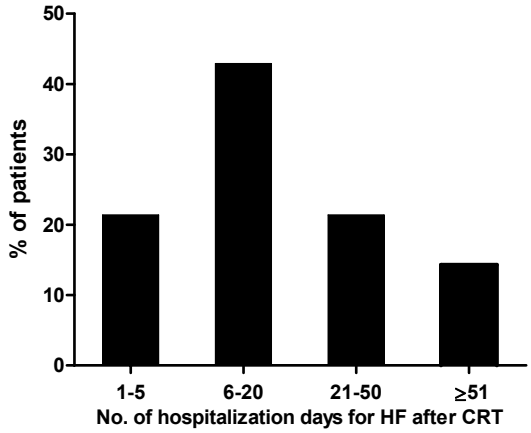

Figure 3. Hospitalizations days in patients admitted for heart failure (HF) after CRT. Out of all patients hospitalized for HF, 21.4% was admitted 1-5 days, 42.9% was admitted 6-20 days, 21.4% was admitted 21-50 days and 14.3% was admitted more than 50 days during follow-up.

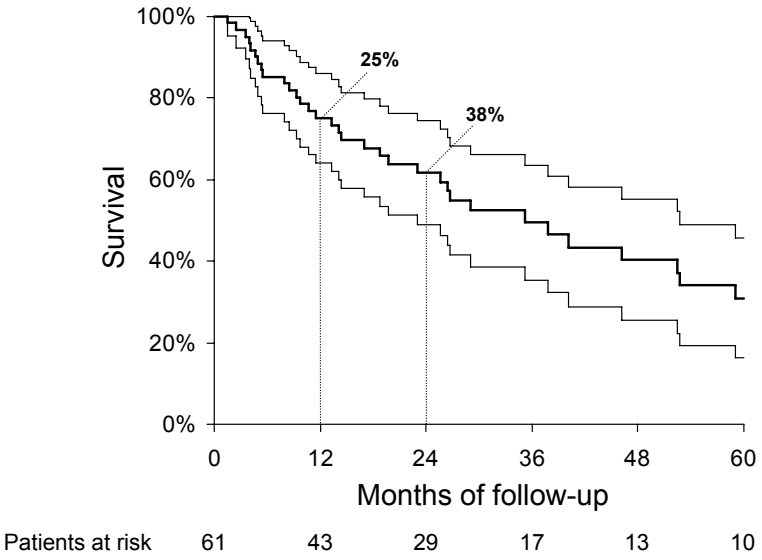

Figure 4. Kaplan-Meier survival curve and corresponding 95% confidence intervals for all-cause mortality after CRT. During a mean follow-up of 30±26 months, 36 patients died, 27 (75%) of which due to worsening heart failure. Respective 1- and 2-year mortality rates were 25% and 38%.

Table 2. Uni- and multivariate Cox proportional hazards models for time to all-cause mortality

	Univariate		**Multivariate**	
Variable	*HR (95%-C.I.)*	*p-value*	*HR (95%-C.I.)*	*p-value*
Age (years)	1.02 (0.98-1.06)	0.318		
Male gender	1.48 (0.67-3.26)	0.330		
Ischemic heart failure	1.13 (0.56-2.26)	0.737		
Resting heart rate	1.01 (0.98-1.04)	0.485		
QRS duration (ms)	1.00 (0.99-1.01)	0.843		
Diabetes	1.62 (0.79-3.35)	0.189		
eGFR (ml/min/1.73m^2)	0.97 (0.95-0.98)	**<0.001**	0.98 (0.96-0.99)	**0.013**
6-minute walk test (m)	0.99 (0.99-1.00)	**0.033**	1.00 (0.99-1.01)	0.592
Quality of Life score	1.03 (1.00-1.05)	**0.043**	1.01 (0.98-1.04)	0.473
LV end-systolic volume (ml)	1.00 (1.00-1.00)	0.959		
LV end-diastolic volume (ml)	1.00 (1.00-1.00)	0.780		
LV ejection fraction (%)	0.99 (0.94-1.03)	0.582		
Mitral regurgitation (grade)	1.51 (1.16-1.97)	**0.002**	1.32 (0.96-1.81)	0.085

C.I. = confidence interval, rest of abbreviations as in Table 1

DISCUSSION

Over the past decade, CRT has become a well-established therapy for patients with advanced heart failure. Large clinical trials have shown improvements in heart failure symptoms, exercise capacity, LV function and survival after initiation of CRT.[11-14] Accordingly, current guidelines recommend a class I indication for CRT implantation in patients with severe heart failure (NYHA functional class III or IV), depressed LVEF (≤35%), and a wide QRS complex (≥120 ms).[2] Although CRT is indicated in patients in NYHA functional class IV, little is known about the true potential effects in this group. Moreover, the large trials in CRT comprised 10.830 patients, of which only 454 (4.2%) were in NYHA functional class IV.[5] In the current study, comprising of 61 patients who presented with symptoms according to NYHA functional class IV heart failure, CRT significantly improved clinical status and LV function. Nonetheless, long-term outcome showed a high mortality, with 1- and 2-year mortality rates of 25% and 38% respectively.

Reported numbers for (1-year) mortality in medically treated NYHA functional class IV patients may be up to 50-60%.[15-17] A sub-study from BEST (Beta-blocker Evaluation of Survival Trial), analyzed 226 patients in NYHA functional class IV, out of the originally enrolled 2708 heart failure patients.[15] Patients were randomized to receive either bucindolol or placebo, and mortality or heart failure hospitalizations were assessed during follow-up. After a mean follow-up of 1.6 years, 49% of the patients had died. Of note, the administration of bucindolol had no beneficial effect on mortality or heart failure hospitalization in this study (Log-Rank 1.03, $p = 0.30$).

In addition, Stevenson et al analyzed 129 patients in NYHA functional class IV, randomized to receive either a left ventricular assist device or optimal medical management in the Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) trial.[16] Patients had end-stage heart failure (mean LVEF 17±8%), as evidenced by a 71% prevalence of intravenous inotropic therapy before randomization. Observed 1-year mortality was 60% in patients randomized to optimal medical management who were not on inotropic therapy before randomization, and as high as 76% in patients who did receive inotropic therapy.

Finally, a recent sub-analysis from the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial examined the outcome of all NYHA functional class IV patients enrolled.[17] In total, 217 patients in NYHA functional class IV were enrolled, of which 55 were randomized to optimal medical therapy. The reported 1-year mortality in this group reached 44% and 2-year mortality rate (adjusted for follow-up time) was 62%. These reported mortality figures in NYHA functional class IV patients on optimal medical therapy clearly demonstrate that these patients generally have a poor prognosis.

Only a few studies explored the effect of CRT in NYHA functional class IV patients. A small observational study by Herweg et al reported a significant decrease in LVESV from 174±65

ml to 150±78 ml (p<0.01), accompanied by a significant increase in LVEF from 24±4% to 32±9% (p<0.05) after initiation of CRT in 10 inotrope-dependent, NYHA functional class IV heart failure patients.[18] More importantly, all 10 patients were alive after a mean follow-up of 1082±284 days. Nonetheless, 3 patients underwent cardiac transplantation after 56, 257 and 910 days respectively. Additionally, Cowburn et al reported a beneficial effect of CRT, also in 10 end-stage heart failure patients on inotropic support.[19] All patients could be taken off inotropic support after 2±2 days and survived until hospital discharge. However, after 361±221 days of follow-up, 3 patients had died and 1 patient underwent cardiac transplantation.

Currently, the largest study on the effects of CRT in patients with NYHA functional class IV heart failure is the earlier mentioned sub-analysis from COMPANION.[17] In this study, the 217 NYHA functional class IV patients enrolled were separately analyzed. A total of 83 (38%) patients were randomized to receive CRT with a defibrillator (CRT-D), 79 (36%) patients received CRT, and 55 (25%) patients received optimal medical therapy (OMT). At 6 months follow-up, significant improvements were noted in the CRT-D/CRT combined group (n = 162) vs. the OMT group. There was an improvement in NYHA functional class in 119 (73%) patients vs. 27 (49%) patients in the OMT group, p<0.01. In addition, there was a reduction in the QoL score of 25 in the CRT-D/CRT combined group, vs. only 4 in the OMT group, p<0.01. More importantly, the primary end-point of time to death or hospitalization for any cause was significantly improved by both CRT (HR 0.64; 95% CI 0.43 - 0.94, p = 0.02) and CRT-D (HR 0.62; 95% CI 0.42 - 0.90, p = 0.01). Patient populations in the COMPANION sub-analysis and the present study are very similar (mean age 67 years in COMPANION vs. 68 years in the current study, both studies report 62% ischemic etiology of heart failure and a mean LVEF of 21±7%). Still, the 1- and 2-year mortality rates for CRT-D treated patients in the sub-analysis from COMPANION were 30% and 55% respectively. Although comparable, this is higher than the presently observed 1- and 2-year mortality rates of 25% and 38%.

An interesting finding in the present study was that eGFR was the only baseline characteristic that was independently associated with all-cause mortality during long-term follow-up. Apparently, in such a selected population, more traditional risk factors like ischemic etiology of heart failure or more depressed LVEF do not exert a further effect on mortality. However, renal function is in general a strong predictor of mortality in patients with (severe) heart failure.[20, 21]

There are several possible explanations for worse outcome in heart failure patients with renal failure that go beyond the scope of the current study. One explanation can be that renal failure is caused by more pronounced forward failure. Another explanation may be that renal failure is a result of increased venous pressure (which is frequently observed in patients with heart failure). The current study confirms that worse renal function is also associated with higher mortality in NYHA functional class IV patients undergoing CRT.

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