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Original Article

Cardiac resynchronization therapy in patients with heart failure and moderately reduced ejection fraction: Could it trigger a super-response?

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ABSTRACT

Background/Aim: Despite the well-established benefits of cardiac resynchronization therapy (CRT) in heart failure (HF) patients with left ventricular ejection fraction (LVEF) ≤35%, many patients with less reduced EF remain refractory to optimized medical treatment and at high risk of morbidity and mortality. The objective of the study is to evaluate the effects of CRT in optimally treated patients with New York Heart Association (NYHA) classes II–IV, LVEF of 36–45%, and left bundle branch (LBBB), including clinical, structural and biochemical response.

Methods: A selected group of HF patients have been implanted with CRT-P devices and were followed up for 6 months at 4, 12 and 24 weeks. Clinical assessment included NYHA class, quality of life and 6-min walk distance (6 MWD) test. Echocardiographic assessment included LV dimensions and function and left atrial volume. Serum N-terminal pro b-type natriuretic peptide (NT-ProBNP) was measured at the same intervals.

Results: This prospective single center study included 23 patients. NYHA functional class significantly improved after CRT-P ($p < 0.0001$), associated with improvement in QOL ($p < 0.0001$) and 6 MWD, which increased, from 145.7 ± 20.1 m to 219.5 ± 42.2 m ($p < 0.0001$). Mean QRS duration showed significant shortening from 164.4 ± 13.2 ms to 126.4 ± 13.6 ms ($p < 0.0001$). CRT induced reverse remodeling with reduction in both left ventricular end diastolic diameter (LVEDD) from 68.95 ± 5.05 mm to 62.8 ± 4.47 mm, $p = 0.0002$ and left ventricular end systolic diameter (LVESD) from 54.1 ± 4.5 mm to 46.5 ± 4.1 mm, $p < 0.0001$, and significant increase in LVEF (from 40.3 ± 2.8 to 48.3 ± 4.2 mm, $p < 0.0001$). The biochemical response to CRT showed significant reduction in serum NT-ProBNP from 1025.6 ± 363.1 pg/ml to 594.9 ± 263.5 pg/ml ($p < 0.0001$).

Conclusions: Symptomatic HF patients on maximal optimized medical treatment who have LBBB and baseline LVEF 35–45% appeared to derive significant clinical and structural benefit from CRT.

1. Introduction

The beneficial effects of cardiac resynchronization therapy (CRT) have been well established in patients with congestive heart failure (CHF) who remain in New York Heart Association (NYHA) classes II–IV, despite the maintenance on guidelines directed optimal medical treatment and have a wide QRS (≥130 ms) and reduced left ventricular ejection fraction (LVEF) (≤35%).[1,2] Subgroup analyses of large trials suggest that the benefits are more established in patients with wider QRS durations and/or left bundle branch block (LBBB),[3–5] and this has been recognized in current guidelines.[6,7] Recently, it has been suggested that CRT may also be beneficial in patients with a moderately impaired LV function (LVEF > 35%)[8–10] by results of post hoc subgroup analysis from the PROSPECT,[8] MADIT-CRT,[9] and REVERSE[10] trials. Many patients with NYHA II–IV CHF with a less reduced LVEF (35–45%) are refractory to optimized medical treatment and remain at high risk of morbidity and mortality, yet with few established other treatment options, and their prognosis is worse in the presence of prolonged QRS complex, especially LBBB.[11,12] We aimed with this study to

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prospectively evaluate the effects of CRT in optimally treated patients with NYHA Classes II–IV CHF, LVEF of 36–45%, and LBBB and whether these outcomes are associated with structural changes in cardiac chambers dimensions and biochemical parameters indicating improved HF status.

2. Methods

2.1. Patient selection

After approval by the 'ethical committee' of Ain-Shams University and the patients' consents, we prospectively included patients with stable symptomatic HF, NYHA class II/IV, despite maximal tolerated medical treatment for at least 6 months, moderate impairment of LV systolic function, with a LVEF = 36–45%, sinus rhythm with a complete LBBB and a QRS duration ≥130 ms, and no history of ventricular arrhythmias or indication for an implantable cardioverter defibrillator (ICD) for secondary prevention during the period from July 2016 to March 2018.

2.2. Study design

The study was a single-center, prospective pilot study where all patients were recruited, underwent device implantation, and followed up at the same center.

At baseline, all patients were subjected to thorough history analysis and clinical examination to define their functional class, quality of life (QOL) assessment, 6-min walk distance (6 MWD) test, 12-lead surface electrocardiogram (ECG), and serum plasma level assessment of N-terminal pro b-type natriuretic peptide (NT-Pro BNP).[13,14]

A transthoracic echocardiographic assessment (TTE) was performed at baseline using a Vivid 7 machine with an M4S matrix sector array probe with a frequency range of 1.5–3.6 MHz (GE Vingmed Ultrasound, Horten, Norway) with the machine-integrated ECG recording connected. The echocardiographic measurements were performed in concordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging[15] and included LV EF (%) in 2D using Modified Simpson's method of discs in the apical four- and two-chamber views. Also left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) using M-mode echocardiography from the parasternal short-axis view at the level of the papillary muscles were measured. The left atrial volume index (LAVI) was also measured in mL/m^2 using the Simpson's method of discs in both apical four- and three-chamber views.

2.3. Device therapy

All patients underwent a CRT-P device implantation; we used commercially available transvenous leads and devices. Standard implantation technique was used with an emphasis on placing the left ventricular lead to the lateral or posterolateral wall of the left ventricle whenever possible. All patients had implanted standard bipolar LV leads. Patients with inaccessible lateral, posterior, or posterolateral vein tributaries of the coronary sinus as well as patients with inadequate thresholds or inappropriate phrenic nerve stimulation were excluded from the study to avoid effects of several cofounding factors on outcome. The atria to ventricle delay and the ventricle to ventricle delays were optimized immediately after implantation using TTE.[16]

2.4. Follow-up evaluation

Patients were seen at follow up visits at 4 weeks, 12 weeks, and 24 weeks after implantation. At each follow-up visit, clinical assessment was performed including the following: NYHA class, QOL evaluation using the Minnesota living with heart failure questionnaire,[17] 6MWD test, QRS duration in milliseconds on 12-lead surface ECG, TTE evaluating the same parameters assessed at baseline studies, and serum level of NT-proBNP in pg/m.

CRT response was defined as an improvement of NYHA class by one class, in addition to decrease in LV end systolic volume (ESV) of ≥15% and/or absolute increase of 5% in LVEF at 6-month visit.[18–20]

2.5. Statistical analysis

Analysis of data was performed using SPSS, version 22.0, SPSS Inc, Chicago, IL. Categorical variables were expressed as numbers or percentages. Description of quantitative variables was obtained as mean ± standard deviation and range. Description of qualitative variables was obtained in the form of frequency and percentage. A quantitative difference in mean values was tested with the Student *t*-test of two independent samples and expressed as *t*-value and *p*-value. Paired *t*-test was used to compare quantitative data in the same group at different intervals. Chi-square and Fisher exact tests for categorical variables are used.

Two-tailed *p* values are presented, with <0.05 designated as statistically significant.

3. Results

Twenty-three patients have been included in our study and formed the basis of the statistical analyses.

3.1. Baseline demographic data

The baseline demographic and clinical characteristics of the studied population are listed in (Table 1).

3.2. Outcome measures

The clinical response of the patients in the study after 6 months from implantation (changes in NYHA functional class, QOL, and 6 MWD), electrocardiographic response (changes in QRS duration), echocardiographic response (changes in LVEDD, LVESD, LVEF, and LAVI), and biochemical response (changes in serum level of NT-ProBNP) are listed in (Table 2).

Patients' clinical response showed significant improvement of all parameters. The NYHA functional class significantly improved after CRT-P ($p < 0.0001$). This was also associated with significant improvement in QOL (from 73.6 ± 8.1 to 54.45 ± 8.34, $p < 0.0001$) and 6 MWD, which significantly increased, from 145.7 ± 20.1 m to 219.5 ± 42.25 m ($p < 0.0001$).

Mean QRS duration showed significant shortening after CRT, decreasing from 164.4 ± 13.2 ms to 126.4 ± 13.69 ms ($p < 0.0001$).

The echocardiographic examination showed reduction in both LVEDD (from 68.95 ± 5.05 mm to 62.8 ± 4.47 mm, $p = 0.0002$) and LVESD (from 54.1 ± 4.48 mm to 46.5 ± 4.09 mm, $p < 0.0001$), which was translated into significant increase in LVEF (from 40.35 ± 2.77 to 48.3 ± 4.16 mm, $p < 0.0001$). The LA volume was significantly reduced as measured by LAVI (from 42.95 ± 3.3 mL/m^2 to 37.8 ± 3.02 mL/m^2, $p < 0.0001$).

The biochemical response to CRT showed significant improvement in serum levels of the NT-Pro BNP which were reduced from 1025.6 ± 363.1 pg/ml to 594.9 ± 263.54 pg/ml ($p < 0.0001$).

Table 1
Baseline demographic and clinical characteristics of the studied group.

Parameter	Result
Age (Years): mean ± SD	61.65 ± 10.54
Gender	
Male, *n* (%)	14 (60%)
Female, *n* (%)	9 (39%)
Etiology of heart failure	
ICM, *n* (%)	10 (43.5%)
DCM, *n* (%)	13 (56.5%)
Risk factors and comorbidities	
DM, *n* (%)	13 (56.5%)
Hypertension, *n* (%)	15 (65.2%)
Obesity, *n* (%)	3 (13%)
Renal impairment, *n* (%)	3 (13%)
COPD, *n* (%)	5 (21.7%)
CLD, *n* (%)	3 (13%)
Drug treatment	
ACEIs/ARBs, *n* (%)	20 (87%)
β blockers, *n* (%)	19 (83%)
Loop diuretics, *n* (%)	21 (91.3%)
MRAs, *n* (%)	18 (78.3%)
Digitalis, *n* (%)	16 (70%)
NYHA class	
II, *n* (%)	3 (13%)
III, *n* (%)	12 (52%)
IV, *n* (%)	8 (35%)
QOL: mean ± SD	73.6 ± 8.1
6 MWD (m): mean ± SD	145.7 ± 20.1
QRS duration (ms): mean ± SD	164.4 ± 13.2
LVEDD (mm): mean ± SD	68.95 ± 5.05
LVESD (mm): mean ± SD	54.1 ± 4.48
LVEF (%): mean ± SD	40.35 ± 2.77
LAVI (mL/m^2): mean ± SD	42.95 ± 3.3
NT-ProBNP (pg/mL): mean ± SD	1025.6 ± 363.1

ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CLD, chronic liver disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; MRA, mineralocorticoid receptor antagonists; QOL, quality of life; 6 MWD, 6-min walk distance test; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; NT-ProBNP: N-terminal pro b-type natriuretic peptide; SD, standard deviation.

The echocardiographic response (changes in LVEDD, LVESD, LVEF, and LAVI), and biochemical response (changes in serum level of NT-Pro BNP) were evaluated after 4 weeks, 12 weeks, and 24 weeks after implantation and the changes in these parameters are shown in (Figs. 1 and 2).

3.3. CRT response

According to the predefined measures for response to CRT, only 2 patients were nonresponders. Both were male patients, one with DCM and the other with ICM, with a mean LVEF = 42.57 ± 2.31 and a mean QRS duration = 128.2 ± 11.49.

There was no statistically significant difference in CRT response based on the etiology of cardiomyopathy in the studied population. Both patients with dilated cardiomyopathy and ischemic cardiomyopathy showed similar response to CRT at the end of the study follow-up (Table 3).

4. Discussion

CRT is an established standard of care for advanced systolic HF patients with evidence for ventricular dyssynchrony as represented by QRS duration ≥120 ms.[1,2] Landmark clinical trials have used LVEF ≤35% as entry criteria, making this cutoff value as a major determinant for patient eligibility for CRT in clinical practice.[1,2]

Table 2
Outcome of different parameters after 6 months of CRT implantation.

Parameter	Baseline	After CRT	*p*-value
NYHA class			
I, *n* (%)	0 (0%)	3 (13%)	<0.0001
II, *n* (%)	3 (13%)	13 (57%)	<0.0001
III, *n* (%)	12 (52%)	5 (22%)	<0.0001
IV, *n* (%)	8 (35%)	2 (8%)	<0.0001
QOL: mean ± SD	73.6 ± 8.1	54.45 ± 8.34	<0.0001
6 MWD (m): mean ± SD	145.7 ± 20.1	219.5 ± 42.25	<0.0001
QRS duration (ms): mean ± SD	164.4 ± 13.2	126.4 ± 13.69	<0.0001
LVEDD (mm): mean ± SD	68.95 ± 5.05	62.8 ± 4.47	0.00022
LVESD (mm): mean ± SD	54.1 ± 4.48	46.5 ± 4.09	<0.0001
LVEF (%): mean ± SD	40.35 ± 2.77	48.3 ± 4.16	<0.0001
LAVI (mL/m^2): mean ± SD	42.95 ± 3.3	37.8 ± 3.02	<0.0001
NT-ProBNP (pg/mL): mean ± SD	1025.6 ± 363.1	594.9 ± 263.54	0.00012

QOL, quality of life; 6 MWD, 6-min walk distance test; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; NT-ProBNP, N-terminal pro b-type natriuretic peptide; SD, standard deviation.

However, there are several considerations that deserve closer consideration of the role of LVEF in patient selection for CRT. Selection of LVEF ≤35% as the entry criterion for HF clinical trials is based on a higher risk of adverse outcomes, particularly sudden cardiac death.[21,22]

LVEF is recognized as a risk predictor for morbidity and mortality in HF patients. While the risk of hospitalization and/or death declines as LVEF increases, an LVEF in the range of 36%–45% still confers a significant risk of adverse outcomes, whereas a higher LVEF does not further contribute to mortality.[21–23] Although excluded from CRT according to current guidelines, there are HF patients with LVEF >35% who may benefit from therapy. Clearly, the disease burden due to HF with preserved systolic function is significant, as nearly 50% of hospitalized patients with HF have a measured LVEF >35%.[24,25]

Taken together, these facts illustrate the need for therapies in this increasing population with mildly reduced LVEF. The present study was conducted to evaluate the different effects (clinical, structural and biochemical) of CRT in a cohort of patients with symptomatic CHF, LBBB, and mildly reduced LV function (LVEF 36–45%).

Over a period of 21 months, 23 eligible patients have been subjected to CRT-P implantation and were followed up for a period of 6 months to evaluate the clinical, echocardiographic, and biochemical response to CRT. Fung et al[26] have included 15 patients with NYHA class III and LBBB, with an LVEF >35% and <45%. They followed the patients for 3 months for both standard HF assessment and echocardiographic examination. More recently, Linde et al have designed a prospective, randomized, controlled, double-blinded study to evaluate CRT-P in NYHA II–III HF patients with LBBB and with LVEF of 36%–50% and no previous pacing or ICD. The primary endpoint was a composite of time to first HF event or death. The MIRACLE EF study was stopped for enrollment futility after 13 months and enrolling only 44 patients.[27]

The present study showed significant improvement in HF symptoms and NYHA functional class. Most patients have improved at least one NYHA class. Furthermore, standard HF assessment using the Minnesota living with heart failure questionnaire and 6 MWD showed significant improvement after CRT ($p < 0.0001$). Fung et al[26] showed significant improvement in NYHA functional class, whereas other HF assessment parameters (QOL score, 6 MWD, exercise capacity in a metabolic equivalents of task (METS) test) did not show significant improvement after 3 months of follow-up. This could be explained by the small number of patients included in the study and shorter period of follow-up. Foley et al[28]

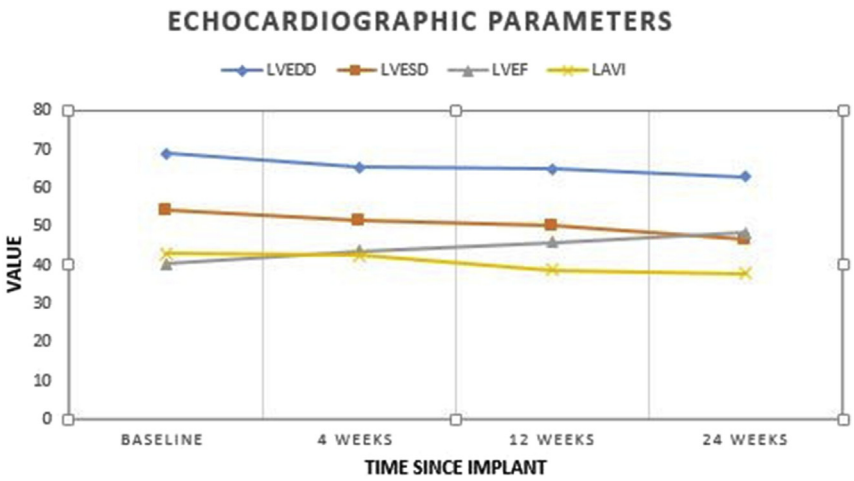

Fig. 1. Echocardiographic response during the first 6 months after CRT. CRT, cardiac resynchronization therapy; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index.

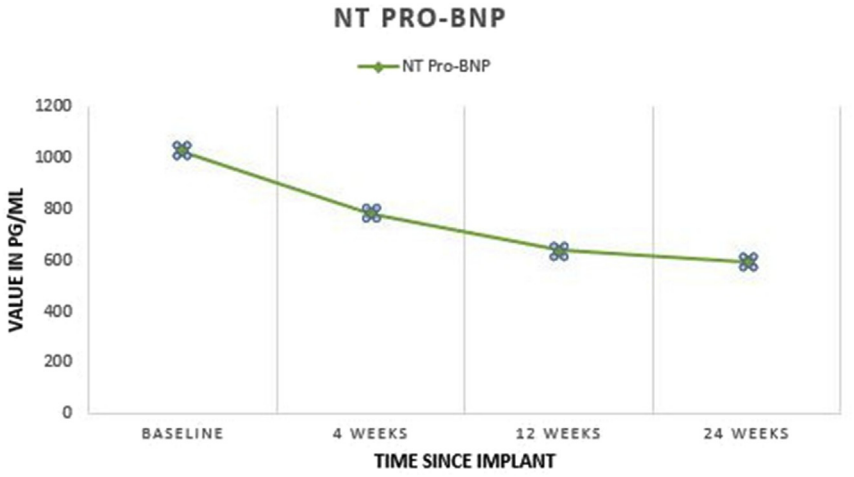

Fig. 2. Biochemical response during the first 6 months after CRT. CRT, cardiac resynchronization therapy; NT-ProBNP, N-terminal pro b-type natriuretic peptide.

Table 3
Response to CRT according to the etiology of cardiomyopathy.

Parameter	DCM		ICM		*p*-value
	Baseline	After CRT	Baseline	After CRT	
NYHA class					
I, *n* (%)	0 (0%)	2 (15.4%)	0 (0%)	1 (10%)	0.134
II, *n* (%)	2 (15.4%)	7 (53.8%)	1 (10%)	6 (60%)	0.716
III, *n* (%)	6 (46.1%)	3 (23.1%)	6 (60%)	2 (20%)	0.35
IV, *n* (%)	5 (38.5%)	1 (7.7%)	3 (30%)	1 (10%)	0.99
QOL: mean ± SD	72.5 ± 2.3	52.8 ± 6.6	74.2 ± 3.0	56.1 ± 8.5	0.329
6 MWD (m): mean ± SD	146.9 ± 5.8	223.9 ± 43.1	143.6 ± 6.9	215.1 ± 41.4	0.625
QRS duration (ms): mean ± SD	167.2 ± 4.7	130.2 ± 14.1	162.8 ± 2.6	122.7 ± 13.2	0.205
LVEDD (mm): mean ± SD	69.2 ± 3.1	63.4 ± 4.5	67.6 ± 4.3	62.1 ± 4.4	0.495
LVESD (mm): mean ± SD	55.2 ± 3.8	47.4 ± 4.1	54.3 ± 5.7	45.6 ± 3.9	0.296
LVEF (%): mean ± SD	40.8 ± 3.4	48.8 ± 4.6	40.2 ± 4.1	47.8 ± 3.9	0.579
LAVI (mL/m^2): mean ± SD	43.2 ± 4.1	38.4 ± 3.5	42.6 ± 2.8	37.2 ± 2.8	0.371
NT-ProBNP (pg/mL): mean ± SD	1037.6 ± 387.2	612.7 ± 271.4	1019.4 ± 346.5	577.1 ± 255.6	0.751

QOL, quality of life; 6 MWD, 6-min walk distance test; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; NT-ProBNP, N-terminal pro b-type natriuretic peptide; SD, standard deviation.

observed similar clinical improvements (NYHA functional class, QOL score, and 6 MWD) in patients with LVEF >35%, compared with patients with LVEF ≤35%. Results of post-hoc analyses of randomized controlled trials of CRT reported comparable CRT benefits in patients with an LVEF >35%[8–10] as in patients with LVEF ≤35%. In a substudy from the PROSPECT trial that included NYHA

III–IV HF patients, Chung et al[8] reported similar benefits from CRT regarding the clinical composite response by Packer and reverse remodeling in patients with LVEF >35% compared to those with LVEF <35%.

The present study shows significant reduction of LV dimensions and LA volume with an associated significant improvement of LV systolic function, as examined by measurement of LVEF using 2D echocardiography. These changes were maintained over the follow-up period of 6 months with continuous improvement of all these parameters over time since CRT implant (see Fig. 1). The improvement of LVEF was linear and reached 19.7% increase after 6 months compared with baseline LVEF demonstrating a super-response in this patient cohort who were selected mainly based on wide baseline QRS complex and morphology of LBBB.

Careful analysis of the REVERSE study revealed that almost 24% of patients had LVEF >30%. After a 24-month follow-up time, CRT in patients with LVEF >30% resulted in a significant 74% relative risk reduction in time to HF hospitalizations or death compared with 42% in the group with LVEF ≤30%. There were also associated reductions in LV ESV index and LV mass in LVEF >30% patients, although not to the same extent as in those with LVEF <30%.[10]

Electrical dyssynchrony is critical for CRT-induced improvements, with previous studies suggesting that response increases with longer intrinsic QRS duration and LBBB morphology.[3,4] Our patients had wide QRS (164.4 ± 13.2 msec), and all patients had LBBB. Coinciding with these findings, a meta-analysis of 5 randomized trials showed that increasing QRS duration at baseline was an independent predictor for response to CRT.[29] These results indicate that the benefits of CRT may be present for patients with QRS prolongation and mild HF with less severe LV dysfunction than previously studied.

LA enlargement is a marker of both the severity and chronicity of diastolic dysfunction and magnitude of LA pressure elevation in patients with HF.[30] In addition, relationships exist between increased LA size and the incidence of atrial fibrillation and stroke, risk of overall mortality after myocardial infarction, and risk of death and hospitalization in patients with dilated cardiomyopathy.[31] In a recent study, we demonstrated that CRT resulted in significant reduction in LA diameter and maximal and minimal LA volumes (LA Vmax and LA Vmin, respectively). This favorable effect of reverse LA remodeling was limited to the cardiac responders group (i.e., those with significant LV reverse remodeling).[32] In the present study, there is significant reduction in LA volume index after CRT in our patient cohort. The reduction was observed after 4 weeks and was evident at 3 months from CRT implantation (see Fig. 1). This early significant reduction in atrial volumes at 3 months was also reported by Vural et al[33] to occur simultaneously with LV reverse remodeling; even more early favorable changes in LA volumes were reported only 1 month after CRT implantation and kept going on until at least 6 months after implantation.[34] These findings can be simply explained by the improvement in LV systolic and diastolic functions and filling pressures and consequently resulting in decrease in LA pressures.

Natriuretic peptides (NPs), specifically BNP and NT-pro BNP, have diagnostic and prognostic values in patients with HF.[35,36] Decreases in BNP during follow-up with various HF therapies are associated with reduced morbidity and mortality outcomes, whereas increasing BNP portends poor patient outcomes.[37–40]

The present study demonstrated significant reduction of the serum levels of NT pro-BNP after CRT ($p < 0.0001$). The reduction was well noticed after 4 weeks of CRT implantation and was maintained throughout the 6 months follow up period (see Fig. 2). The CARE-HF study demonstrated that CRT exerts a remarkable early and sustained reduction in plasma concentrations of NT-pro-BNP levels when compared with pharmacological therapy alone in patients with moderate to severe chronic HF and markers of ventricular dyssynchrony.[39] The early reduction in NT-pro-BNP observed in CARE-HF and in our study probably reflects the acute hemodynamic improvement after CRT. This is translated into reduction in ventricular filling pressure and improved efficiency with subsequent ventricular reverse remodeling. Later, analysis by Fruhwald et al[40] confirmed these observations and demonstrated that CRT resulted in an early and sustained reduction in NT-pro-BNP that was associated with early and progressive improvement in echocardiographic LV parameters. Therefore, NT-pro-BNP may be a useful additional marker of monitoring the effects of CRT especially in early postimplantation period.

Several reports have demonstrated criteria of responder patients to CRT, including female sex, nonischemic etiology of cardiomyopathy, LBBB, and QRS duration ≥150 msec.[7,41,42]

The results of our study did not show such significant differences in outcomes among both sexes and patients with ischemic or nonischemic cardiomyopathy, probably because of small sample size, well-selected patients at entry with LBBB, and wide QRS complex >150 msec (see Table 3).

5. Conclusions

In this prospective single-center study, symptomatic HF patients on maximal optimized medical treatment who have LBBB and a baseline LVEF 35–45% appeared to derive significant clinical and structural benefit from CRT.

However, before expanding indications for CRT to include patients with less severe LV systolic dysfunction, randomized prospective studies to evaluate the effect of CRT on such important group of HF patients are needed. Furthermore, long-term follow-up is needed to demonstrate morbidity and mortality improvements on top of existing medical therapy in such relatively lower risk HF population.

5.1. Study limitations

The major limitation of the present study is the small sample size and nonrandomized design. Larger randomized studies with a crossover design would be a more beneficial approach to start examining a potentially new indication for CRT in such an important sector of HF patients.

Compliance with ethical standards

This study was approved by our ethical committee, and an informed consent was obtained from all patients before their inclusion in the study.

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Conflict of interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2019.04.010.

References

1. Moss AJ, Hall WJ, Cannom DS, et al, MADITCRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329–1338.
2. Tang AS, Wells GA, Talajic M, et al, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363:2385–2395.
3. Zareba W, Klein H, Cygankiewicz I, et al, MADITCRT Investigators. Effectiveness of cardiac resynchronization therapy by QRS morphology in the multicenter automatic defibrillator implantation trial — cardiac resynchronization therapy (MADIT-CRT). *Circulation*. 2011;123:1061–1072.
4. Gold M, Thébault C, Linde C, et al. The effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the resynchronization reverses remodeling in systolic left ventricular dysfunction (REVERSE) study. *Circulation*. 2012;126:822–829.
5. Birnie DH, Ha A, Higginson L, et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail*. 2013;6:1190–1198.
6. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Heart Rhythm*. 2012;9:1737–1753.
7. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace*. 2013;15:1070–1111.
8. Chung ES, Katra RP, Ghio S, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. *Eur J Heart Fail*. 2010;12:581–587.
9. Kutyifa V, Kloppe A, Zareba W, et al. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy. *J Am Coll Cardiol*. 2013;61:936–944.
10. Linde C, Daubert C, Abraham WT, et al. On behalf of the resynchronization reverses remodeling in systolic left ventricular dysfunction (REVERSE) study group: impact of ejection fraction on the clinical response to cardiac resynchronization therapy in mild heart failure. *Circ Heart Fail*. 2013;6:1180–1189.
11. Lund L, Jurga J, Edner M, et al. Prevalence correlates and prognostic significance of QRS prolongation in patients with heart failure with reduced and preserved ejection fraction. *Eur Heart J*. 2013;34:529–539.
12. Hawkins NM, Wang D, McMurray JJV, et al, for the CHARM Investigators and Committees. Prevalence and prognostic impact of bundle branch block in patients with heart failure: evidence from the CHARM programme. *Eur J Heart Fail*. 2007;9:510–517.
13. Fuat A, Murphy JJ, Hungin APS, et al. The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. *Br J Gen Pract*. 2006;56:327–333.
14. Kelder JC, Cramer MJ, Verweij WM, et al. Clinical utility of three B-type natriuretic peptide assays for the initial diagnostic assessment of new slow-onset heart failure. *J Card Fail*. 2011;17:729–734.
15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16:233–270.
16. Brabham WW, Gold MR. The role of AV and VV optimization for CRT. *J Arrhythmia*. 2013;29:153–161.
17. Rector RS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure. II. Content, reliability, and validity of a new measure the Minnesota Living with Heart Failure Questionnaire. *Heart Fail*. 1987;3:198–209.
18. Daubert JC, Saxon L, Adamson PB, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. *Europace*. 2012;14(9):1236–1286.
19. Park MY, Altman RK, Orencole M, et al. Characteristics of responders to cardiac resynchronization therapy: the impact of echocardiographic left ventricular volume. *Clin Cardiol*. 2012;35(12):777–780.
20. Tomassoni G. How to define cardiac resynchronization therapy response. *J Innov Card Rhythm Manag*. 2016;7:S1–S7.
21. Solomon SD, Anavekar N, Skali H, et al, Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*. 2005;112:3738–3744.
22. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guidelines for the management of heart failure: a report of the American College of cardiology foundation/American Heart Association Task Force of practise guidelines. *Circulation*. 2013;128:1810–1852.
23. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J*. 2006;27:65–75.
24. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, 586 E.S. Chung et al. treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. *J Am Coll Cardiol*. 2007;50:768–777.
25. Yancy CW, Lopatin M, Stevenson LW, et al, ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the acute decompensated heart failure national registry (ADHERE) database. *J Am Coll Cardiol*. 2006;47:76–84.
26. Fung JW, Zhang Q, Yip GW, et al. Effect of cardiac resynchronization therapy in patients with moderate left ventricular systolic dysfunction and wide QRS complex: a prospective study. *J Cardiovasc Electrophysiol*. 2006;17:1288–1292.
27. Linde C, Curtis AB, Fonarow GC, et al. Cardiac resynchronization therapy in chronic heart failure with moderately reduced left ventricular ejection fraction: lessons from the Multicenter InSync Randomized Clinical Evaluation MIRACLE EF study. *Int J Cardiol*. 2016;202:349–355.
28. Foley PW, Stegemann B, Smith RE, et al. Cardiac resynchronization therapy in patients with mildly impaired left ventricular function. *Pacing Clin Electrophysiol*. 2009;32(suppl 1):S186–S189.
29. Cleland JG, Abraham WT, Linde C, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J*. 2013;34(46):3547–3556.
30. Thomas L, Levett K, Boyd A, et al. Compensatory changes in atrial volumes with normal aging: is atrial enlargement inevitable? *J Am Coll Cardiol*. 2002;40:1630–1635.
31. Moller JE, Hillis GS, Oh JK, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. *Circulation*. 2003;107:2207–2212.
32. Badran HA, Abdelhamid MA, Ibrahim MT, et al. Left atrium in cardiac resynchronization therapy: active participant or innocent bystander. *J Saudi Heart Assoc*. 2017;29:259–269.
33. Vural A, Ağaçdiken A, Ural D, et al. Effect of cardiac resynchronization therapy on left atrial reverse remodeling and spontaneous echo contrast. *Tokohu J Exp Med*. 2004;202:143–153.
34. Yu CM, Fang F, Zhang Q, et al. Improvement of atrial function and atrial reverse remodeling after cardiac resynchronization therapy for heart failure. *J Am Coll Cardiol*. 2007;50:778–785.
35. Cleland JG, McMurray JJ, Kjekshus J, et al, CORONA Study Group. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). *J Am Coll Cardiol*. 2009;54:1850–1859.
36. Savarese G, Musella F, D'Amore, et al. Changes of natriuretic peptides predict hospital admissions in patients with chronic heart failure: a meta-analysis. *J Am Coll Cardiol Heart Fail*. 2014;2:148–158.
37. Wessler BS, Kramer DG, Kelly JL, et al. Drug and device effects on peak oxygen consumption, 6-minute walk distance, and natriuretic peptides as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction. *Circ Heart Fail*. 2011;4:578–588.
38. McMurray JJ, Paker M, Desai AS, et al, PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for a design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2013;15:1062–1073.
39. Cleland JG, Daubert JC, Erdmann E, et al, For the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549.
40. Fruhwald FM, Fahrleitner-Pammer A, Berger R, et al. Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony. *Eur Heart J*. 2007;28:1592–1597.
41. Arshad A, Moss AJ, Foster E, et al, MADIT-CRT Executive Committee. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. *J Am Coll Cardiol*. 2011;57:813–820.
42. Barsheshet A, Goldenberg I, Moss AJ, et al. Response to preventive cardiac resynchronization therapy in patients with ischaemic and nonischaemic cardiomyopathy in MADIT-CRT. *Eur Heart J*. 2011;32:1622–1630.