

## Evaluation of Left Ventricular Systolic Function after Cardiac Resynchronization Therapy in Heart Failure Patients

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Article information	Abstract
<p>Article history: Received: 14 Jan 2013 Accepted: 26 May 2013 Available online: 20 July 2013 ZJRMS 2013; 15(9): 18-22</p> <p>Keywords: Cardiac resynchronization therapy Ventricular ejection fraction Heart failure Echocardiography</p> <p>*Corresponding author at: Cardiovascular Research Center, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran. E-mail: kheirkhah_jalal@yahoo.com</p>	<p><b>Background:</b> Cardiac resynchronization therapy (CRT) has introduced as new treatment strategy in heart failure (HF) patients and some of its effects have been investigated. The aim of this study was to study the effectiveness of CRT in the improvement of left ventricular systolic function indicated by left ventricular ejection fraction (LVEF) in HF patients.</p> <p><b>Materials and Methods:</b> In our prospective study 22 HF patients with NYHA class III and above, QRS duration &gt;120 ms and EF (ejection fraction) ≤35% who were candidates for CRT enrolled. Patients were evaluated for NYHA class, QRS width, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV) and LVEF before and two months after the CRT procedure. Paired-t test analysis used to compare the before and post-CRT data statistically.</p> <p><b>Results:</b> Initial evaluation showed that all of the patients were in NYHA class III before CRT. Two months after CRT, all of the patients improved their NYHA class in a way that 18 patients (82%) were in NYHA class I and the other 4 (18%) were in NYHA class II. The mean (SD) QRS width decreased significantly after biventricular (BiV) pacing (<math>p &lt; 0.001</math>). Also a significant decrease in LVESV, LVEDV and increase in LVEF was shown in HF patients after CRT (<math>p &lt; 0.001</math>).</p> <p><b>Conclusion:</b> The present study showed the efficacy of CRT in improvement of LVEF in HF patients with wide QRS after two months from CRT</p> <p>Copyright © 2013 Zahedan University of Medical Sciences. All rights reserved.</p>

### Introduction

Cardiovascular diseases are considered the first death-leading cause in Iran and congestive heart failure (HF) is a single cardiovascular disease with increasing incidence and prevalence [1] which is associated with a poor quality of life and a high mortality rate [2]. Despite advances in drug treatment, HF is a major worldwide health problem which is the first cause of hospitalization for medical patients and has affected more than a million elderly adults in the United States [1, 3].

Treatment for HF is complicated, and the patients should take a large number of drugs that may be out of their compliance [1, 4]. Despite recent improvements in medical treatments, the prevalence of congestive HF is increasing [1, 5]. It has been estimated that 30% of patients with severe HF have intraventricular conduction delays indicated by a prolonged QRS duration and impaired systolic function with a disorganized ventricular contraction and relaxation pattern [6, 7]. This electromechanical delay in ventricular contraction may be partially overcome by a novel therapeutic method which has been emerged in recent years with the name of biventricular (BiV) pacing or cardiac resynchronization therapy (CRT) [6].

It has been well documented that left ventricular (LV) function delay caused by intraventricular conduction disturbances can induce discoordinated myocardial contraction and consecutively to disorganized myocardial systolic and diastolic function [3, 8] and reduce the pumping effectiveness of the heart [9, 10]. These have been linked with a poor outcome in HF [11-13] and the desynchronized LV function exaggerates clinical symptoms of HF [9].

Some survey have shown that CRT using BiV pacing could be a promising technique with benefits in patients with New York Heart Association (NYHA) class III or above, left ventricular ejection fraction (LVEF) less than or equal to 35% and [14-18], widened QRS despite optimal pharmacological therapy. However, some investigations showed that up to 30% of patients receiving CRT do not have a positive clinical or reverse remodeling response [19].

A decrease in LVEF is clinically had a high sensitivity and specificity for the prediction of long-term all-cause and cardiovascular mortalities. LV remodeling seems to be the strongest predictor of long-term survival after CRT. Therefore, volumetric assessment is not only a surrogate marker of a favorable cardiac response to CRT,

but also an objective measure that predicts long-term clinical outcomes [20].

As a majority of severe HF patients do not get enough benefits from medical therapy and considering the role of LVEF in predicting the response of patients to CRT, in the present study we have investigated the effect of CRT in LVEF in HF patients with NYHA class III or above as a probable beneficial therapeutic strategy in severe HF patients.

## Materials and Methods

In this prospective study, symptomatic HF patients with NYHA class III and above, evidence of LV systolic dysfunction with  $QRS \geq 120$  ms who were admitted in Heshmat Educational Hospital in Rasht city -north of Iran- (from June 2011 till June 2012) and planned for BiV pacing were enrolled. The informed written consents were taken from the all patients.

Patients with  $LVEF > 35\%$  who got benefit from medical therapy or had the history of cardiac or cerebral ischemic event within the previous three months and those HF patients who didn't give consent to register in the survey were excluded.

Patients meeting the criteria for entry underwent initial evaluations for NYHA class, QRS interval (based on leads II, V1 and V6 from a 12-lead electrocardiogram), two-dimensional and Doppler-flow echocardiography. The LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LVEF were assessed by biplane Simpson's equation using the apical four-chamber and two-chamber views where the length of the ventricular image was maximized [14]. Echocardiographic biplane Simpson's method has been validated in the literature by many studies [21]. The advantages of this method compared with other methods are availability, low cost, less complication, non-ionization exposure. These evaluations were performed before and 2 months after CRT.

For this reason, after these initial evaluations, the patients underwent implantation of a cardiac-resynchronization device along with three pacing leads: A standard right atrial (RA) lead, a standard right ventricular (RV) lead, and a specialized left ventricular (LV) lead. RA and RV leads were placed through subclavian vein and LV lead was inserted by a transvenous approach through the coronary sinus into either the posterior or posterolateral cardiac vein.

All patients successfully received BiV pacemakers and no patient was excluded because of unsuccessful implantation. The protocol of the study was approved by Research Ethical Committee of Guilan University of Medical Sciences.

Data were entered in SPSS-16 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean and standard deviation ( $Mean \pm SD$ ). Changes in continuous variables from baseline to follow-up were analyzed using paired Student's *t*-tests. A *p*-value  $< 0.05$  was considered statistically significant.

## Results

Totally, 22 HF patients with wide QRS complex and NYHA class III and above entered the survey. The mean age of the patients was  $60 \pm 13$  years old, 16 (73%) of whom were males and 6 (27%) were females. Totally 9 patients (41%) had mild MR (MR volume  $< 30\%$ ), while 13 patients (59%) had moderate and severe MR (MR volume  $> 30\%$ ). Table 1 shows the initial demographic, hemodynamic and echocardiographic data of all patients.

Initial evaluation showed that all of the patients were in NYHA class III before CRT. Two months after CRT, 18 patients (82%) were in NYHA class I and the other 4 (18%) were in NYHA class II.

The mean (SD) QRS width decreased significantly after BiV pacing ( $p < 0.001$ , Table 2). Also a significant decrease in LVESV and LVEDV was shown in HF patients two months after CRT ( $p < 0.001$ , Table 2). So LVEF which is calculated by  $LVEDV$  minus LVESV divided by LVEDV (%) increased significantly after CRT insertion ( $p < 0.001$ , Table 2).

**Table1.** Demographic, hemodynamic and echocardiographic data of heart failure patients

Variables	Mean $\pm$ SD
Age (year)	$60 \pm 13$
QRS width (ms)	$125 \pm 4$
LVEF (%)	$20.4 \pm 5.8$
MR volume (cc)	$46.9 \pm 30.2$
MR fraction (%)	$40.1 \pm 25.5$
MV area (cm <sup>2</sup> )	$10.6 \pm 3.0$

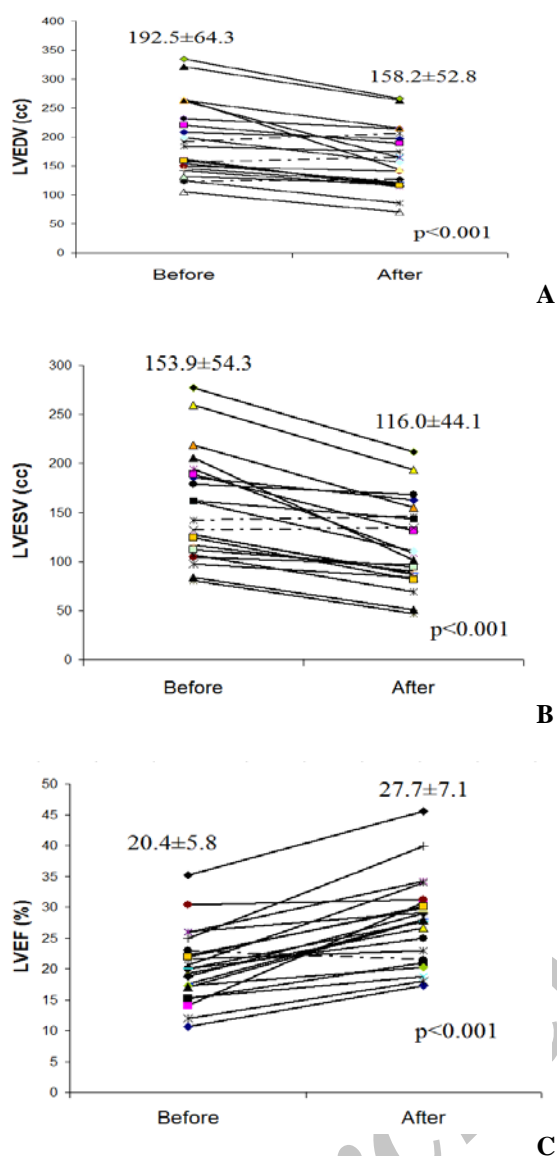
LVEF: Left Ventricular Ejection Fraction, MR: Mitral Regurgitation, MV: Mitral Valve

**Table2.** Comparison of mean (SD) QRS duration, LVESV, LVEDV, LVEF in HF patients before and after CRT

Variables	Before CRT	After CRT	<i>p</i> -Value
QRS duration	$125 \pm 4$	$105 \pm 4$	$< 0.001$
LVESV (cc)	$153.9 \pm 54.3$	$116.0 \pm 44.1$	$< 0.001$
LVEDV (cc)	$192.5 \pm 64.3$	$158.2 \pm 52.8$	$< 0.001$
LVEF (%)	$20.4 \pm 5.8$	$27.7 \pm 7.1$	$< 0.001$

LVESV: Left Ventricular End-Systolic Volume, LVEDV: Left Ventricular End-Diastolic Volume, LVEF: Left Ventricular Ejection Fraction

BiV pacing significantly decreased QRS width, LVEDV (in 19 of 22 patients and a small increase was observed in 3 patients after 2 months from CRT), LVESV (in 20 of 22 patients and a small increase was observed in two patients after CRT) and LVEF (in 21 of 22 patients and a small decrease was observed only in one patients after CRT). Individual changes in LVEDV, LVESV and LVEF between baseline and post CRT in all study patients presented in figure 1 (A, B, C).



**Figure 1.** Individual changes in LVEDV (A), LVESV (B) and LVEF (C) between baseline and post-CRT in all study patients. A small increase in LVEDV and LVESV were observed in three and two patients respectively after CRT (dashed lines) and a small decrease in LVEF was observed in one patient after CRT (dashed line)

## Discussion

As fetal hemoglobin induction considers as novel BiV pacing, or cardiac resynchronization therapy, was proposed nearly 10 years ago as an adjunctive treatment for patients with advanced HF complicated by discoordinate contraction due to intraventricular conduction delay. Since then, growing number clinical trials have studied on the efficacy of this method, with encouraging results [22].

In the present study we also demonstrated some benefits of CRT in severe HF patients and showed that CRT reduced the degree of ventricular dyssynchrony (as evidenced by a shortened duration of the QRS interval), and this effect was accompanied by both an increase in

the LVEF and a decrease in the NYHA class in HF patients with wide QRS and NYHA class III. Some trials have demonstrated significant improvements in NYHA class, quality of life score, and LV function following CRT [6, 9, 14-17, 23, 24]. Gras et al. showed a 5-10% increase in LVEF after CRT in HF patients [24]. Linde et al. reported a 50% improvement in LVEF and an 8-14% decrease in QRS duration after CRT in HF patients [6]. In the present study we found 36% improvement in LVEF and 16% decrease in QRS duration.

Data from the MIRACLE trial showed that the number of non-responders ranged from 12% to 20% according to patient's perception [15]. At the Leiden university medical center 22% of the CRT patients did not improve in functional NYHA class after 6 months of CRT therapy [25]. In the current survey we did not find any non-responders and all the participants showed NYHA class improvement after 2 months of CRT. The differences between various investigations may be due to different methods, time duration following CRT and sampling.

Three mechanisms have been identified underlying the benefit of CRT: Firstly, atrio-ventricular (AV) sequential pacing allows for optimization of the AV-delay resulting in an improvement in systolic function. Auricchio et al. concluded that patients with a wide surface QRS complex had maximum acute benefit when a patient-specific AV-delay was programmed [9]. The second mechanism is shortening the interventricular conduction delay by CRT, resulting in a reduction of the RV-LV dyssynchrony. And thirdly, CRT reverses intraventricular conduction delay which is mainly caused by mechanical dispersion of the motion between the septum and the lateral wall. Yu et al. have shown a decrease in LV dyssynchrony (assessed by tissue Doppler imaging) after CRT [26]. So A-V optimization and the restoration of interventricular and intraventricular synchrony all contribute to the beneficial effects observed after CRT (improvement of systolic function, reduction of mitral regurgitation, reverse remodeling) [25].

We might speculate that an increased systolic function following CRT may have unfavorable results. Because studies of drugs with inotropic effect indicated to a worse survival as a result of increased contractility could be the result of an increase in sympathetic nerve activity. However, in some previous studies of an electromechanical intervention, the significant decrease in heart rate as by the normal sinus node during CRT could be interpreted as an indirect sign of a lesser activation of the sympathetic nervous system. So we can interpret that the most parts of CRT influence on ventricular contractility are related to the mechanisms other than the increase of sympathetic nerve activity [6].

On our best knowledge, the present study is the one of the few studies on the efficacy of CRT in LVEF in HF patients with wide QRS in Iran. However there are some limitations in this survey. The current study is an observational and uncontrolled investigation and the low sample size might interfere with the results; though statistical sample calculation showed that in this study the

sample size is enough and adequately powered to show differences between the measurements before and after CRT. Also the present study investigated the acute effects of CRT in HF patients and the chronic long-term effects still need future researches.

CRT appears promising in terms of improving a patient's clinical symptoms, although the impact on mortality is unknown. Hemodynamic and clinical improvements were demonstrated only in patients in NYHA functional class III or IV, with normal sinus rhythm and results with other HF groups may differ [9]. So future randomized controlled clinical trials should focus on different groups with HF to analyze the efficacy of CRT on various patients with HF.

So our investigation supports the efficacy of CRT on the improvement of LVEF in patients with HF. As LVEF is a sensitive marker of LV function and the majority of severe HF patients may not get enough benefit from medical therapy for their LV dysfunction, this novel

treatment can improve their disease condition significantly.

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### Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

### Conflict of Interest

The authors declare no conflict of interest.

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