Research Article

Cardiac Resynchronization Therapy in Patients with advanced Heart Failure & wide QRS complex in Ibn Al Bitar hospital for cardiac surgery

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Abstract

Background: Evidence suggests that Cardiac Resynchronization Therapy (CRT) is useful in patients with advanced heart failure (HF) & wide QRS complexes despite optimal medical therapy

Objective: To demonstrate the beneficial effect of CRT in improving the hemodynamic profile of patients with advanced HF despite optimal medical therapy.

Methods: This prospective study enrolled 22 patients with advanced heart failure (HF) who were selected from those patients who attend Ibn Al-Bitar center for cardiac surgery during the period from September 2010 to April 2011. All patients were subjected to thorough history taking and physical examination and have been investigated to assess their eligibility to CRT.ECG and Echocardiography {assessing LV systolic & diastolic functions, septal to posterior wall motion delay (SPWMD), left ventricular volumes, left ventricle ejection fraction (LVEF) (by biplane Simpson's method) and mitral regurgitation (MR)} had been done to all patients before and 1 day after CRT device implantation. Tei index calculated before and after CRT, comparing responders and non-responders.

Results: Sixteen patients (72.7%) are matching the definition of the responders. The responders have a decrease in QRS width (by 14.63%), LV end-diastolic diameter (by 6.35%), Tei index (by 14.85%), LV end-systolic volume (16.61%), and SPWMD (by 41.72%) with increase in EF (by 22.86%) in comparison to the non-responder.Also responders patients had higher mean initial Tei index (1.040) in comparison to non-responders whose their mean initial Tei index was (0.9616).

Conclusions: CRT has been shown to improve the functional status in a majority of patients with drug –refractory Heart failure (ischemic, or dilated cardiomyopathy), and Wide QRS complex & resulted in decrease rate of hospitalization in responders.

Keywords: Resynchronization, Therapy Heart Failure , wide QRS complex

INTRODUCTION

The prevalence of heart failure (HF) has increased considerably in the past two decades as a result of better medical therapy of LV dysfunction. Unfortunately, medical therapy is not completely effective in preventing or reversing progression of HF and, as a result, patients with advanced HF have limited options. A Subset of patients with systolic left ventricular dysfunction (LVD) who have associated ventricular conduction delay is at highest risk for HF progression and poor overall outcome. Since the late 1970s, various investigators have shown that

LBBB, RV pacing, or intraventricular conduction defect (IVCD) is associated with a less favorable hemodynamic profile in those with LVD and even in normal subjects.(1) The mechanism for this phenomenon is thought to be due to asynchronous and inefficient contraction of opposing areas of the ventricular myocardium. More importantly, *restoring synchronization, either via simultaneous pacing of the RV apex and the LV free wall or with timed LV free wall activation, can lead to a significant hemodynamic improvement.(1)*

In 1994, two investigators in Europe applied Cardiac Resynchronization Therapy (CRT) in the clinical setting for the first time. Subsequent small observational studies suggested benefit from synchronous pacing. Larger randomized clinical trials confirmed those findings. CRT was approved for maximally medically managed patients with NYHA class III or IV HF symptoms due to severe LV dysfunction associated with prolonged QRS duration. Further randomized studies, powered for mortality, showed a significant survival benefit with CRT or combination of CRT with a defibrillator (CRT-D). (1)

Effects of Cardiac Resynchronization Therapy

A. Impact of CRT on symptoms & exercise tolerance
B. Impact of CRT on morbidity
C. Impact of CRT on mortality
D. Impact of CRT on cardiac structure & function
E. Significant improvement in MR[(2)]

Myocardial performance index (TEI INDEX)

The myocardial performance index (MPI) is a Doppler-derived integrated measure of ventricular systolic and diastolic function.

It has been the subject of much interest since its inception in 1995, and has been well received for its ability to assess both LV and RV function in a variety of patients—heart failure, cardiomyopathy, coronary heart disease, heart transplantation, and in prospective clinical trials.

It is reproducible, easy to measure and can predict morbidity and mortality in patients with cardiomyopathy and heart failure. When applied to the LV, it is the sum of the isovolumic contraction and relaxation times (ICT + IRT) divided by the ejection time.

These measurements are obtained by Doppler assessment of both LV inflow and outflow and using the formula :

Left Ventricular MPI =(ICT + IRT) /ET.[3]

Normal MPI is less than 0.40 with progressively greater values implying progressively worse ventricular function.[4]

The aim of this study is to demonstrate the beneficial effect of CRT in improving the hemodynamic profile of patients with advanced Heart failure despite optimal medical therapy.

PATIENTS AND METHODS

This prospective study enrolled 22 patients with advanced HF who were selected from those patients who attend Ibn Al-Bitar center for Heart Disease during the period from September 2010 to April 2011.

All patients were subjected to thorough history taking and physical examination and have been investigated to assess their eligibility to CRT.

ECG and Echocardiography had been done to all patients before and 1 day after CRT device implantation.

All CRT procedures were done by single operator.

Patients were included if they met the following inclusion criteria:

1) LV dysfunction; LVEF≤35%
2) NYHA class III-IV (ambulatory)HF
3) QRS width 120 ms or more

Patients who were excluded:

1) Severely dyspnoeic and orthopnoeic patients
2) Patients who required hospitalization in the last one month
3) Limited life expectancy
4) Correctable valvular heart disease.

At the time of CRT implantation, all patients were receiving optimal medications, including beta-blockers, ACE-I, loop diuretics, +/- spironolactone as tolerated.

Severity of Heart failure was assessed by New York Heart Association (NYHA) Functional Classification**.** Standard 2-D and Doppler echocardiographic examinations were performed using an HD 7 echocardiographic machine (Philips, the Netherland) before biventricular pacing and at 1 day after CRT implantation and subsequently thereafter. Left ventricular systolic diameter and septal to posterior wall motion delay (SPWMD) were assessed from parasternal long axis view.

Left ventricular volumes, LV ejection fraction (LVEF) (by biplane Simpson's method) and MR were assessed from the apical 4- and 2-chamber view.

LV diastolic function was assessed by pulse-wave Doppler echo of mitral inflow velocity.

The LV Tei index was derived from the mitral inflow and LV outflow tract velocity time intervals.The interval a (determined by measuring the time from the cessation of mitral inflow to the onset of mitral inflow) corresponds to the sum of the isovolumic contraction time (ICT), ejection time (ET), and isovolumic relaxation time (IRT). The interval b (determined by measuring the time interval from the onset of the LV outflow tract flow to the cessation of the LV outflow tract flow) corresponds to LV outflow ejection time (ET).A and B intervals from three consecutive cycles were measured & averaged.The LV Tei index was calculated as (a-b)/b, representing (ICT+IRT)/ET.

All patients were programmed to forcedly pacing both ventricles by setting the AV interval to 130 msec and achieving at least 85% of the time pacing.

Definitions of favorable responses to CRT**:**

i. **Responders:** a patient was classified as being responder to CRT if the LV end-systolic volume decreased by more than 10% at follow-up, or if the NYHA class improved by at least 1 grade, and patient did not require hospitalization for HF symptoms.

ii. **Nonresponders:** Patients with neither LVESV nor NYHA class improvement or who were hospitalized for HF symptoms after CRT.

Data were expressed as mean ± standard deviation. Paired T-test, independent T-test and Chi-square test were used to analyze the result.Statistical significance were defined as P –value ≤ 0.05

RESULTS

This prospective study had enrolled twenty two patients with advanced heart failure, 17(77.27%) were males and 5 (22.72%) were females, with mean age of 51.31± 12.7 years, range 28-80 years. Seven patients (31.81%) had ischemic cardiomyopathy (CMP), fourteen patients (63.63%) had idiopathic dilated CMP, and one patient (4.54%) had hypertrophic cardiomyopathy (HCM). The duration of heart failure ranged from six months to eight years.Twenty one patients received a biventricular pacemaker, and one patient had already an implanted device (pacemaker) underwent upgrading to CRT. Seven patients had an integrated defibrillator with resynchronization.

Table 1 shows the clinical characteristic of patients enrolled in our study about three-quarters of the study group were males and one quarter were females with no statistically significant difference in gender regarding response to CRT (p-value was 0.93).The table also shows that two-thirds of patients had dilated CMP & one third had ischemic CMP, also with no statically significant difference between these two groups regarding response to CRT (p-value 0.84).

Table 2 shows that all patients were in NYHA functional class III-IV. Following CRT implantation, sixteen patients (72.72%) showed improvement in their functional class (NYHA responders defined as reduction in one class; no hospitalization for HF) in comparison to six patients who either remained in the same NYHA class or required hospitalization for HF.

Table 3 shows that eighteen patients enrolled (81.81%) were in sinus rhythm, and four patients (18.18%) had AF.Twenty patients (90.90%) had LBBB, 2 (9.09%) had RBBB.

The mean QRS duration was 128.86 msec that decreased after CRT implantation to 115.71 msec, revealing a 10.20% decrease in the mean of QRS width

Table 4 shows that after CRT implantation, the mean LV end diastolic diameter reduced by 4.82%, EF improved by about 22.65%, A-value reduced by 7.66%, while B-value remains almost the same with just 1.5% reduction which is statically non-significant (p-value 0.79).Tei index which is increased by about 14.85% over the period of follow up.LV end-systolic volume reduced by 11.22% in comparison to pre implant.

SPWMD measured in msec reduced by 36.01%, with a statistically significant reduction after CRT (p-value=0.05). *Table* 5 shows that sixteen patients (72.72%) are matching the definition of the responders while six patients (27.27%) are not.

The responders had a decrease in QRS width (by 14.63%), LV end-diastolic diameter (by 6.35%), Tei index (by 14.85%), LV end-systolic volume (16.61%), and SPWMD (by 41.72%) with an improved EF (by 22.86%) in comparison to the non-responder who showed an increase in QRS width (by 0.88%), a decrease in LV end-diastolic diameter (by 1.24%), Tei index (by 13.86%), and SPWMD (by 20.78%).

Table 1: Baseline Clinical characteristic of the patients

		All patients		Responder		Nonresponder		p-value
		No. (22)	%	No. (16)	%	No. (6)	%	
Age(mean±STD)		51.31 ±12.7		53.5 ±2.9		44.83 ±14.25		0.21
Gender	Male	17	77.27%	13	76.47%	4	23.52%	0.62
	Female	5	22.72%	3	60%	2	40%	
Risk factors	Hypertension	7	31.81%	6	85.71%	1	14.28%	0.005
	Diabetes	6	27.27%	4	66.66%	2	33.3%	
	Smoking	1	4.54%	0	0%	1	100%	
	IHD	7	31.81%	7	100%	0	0%	
Etiology Of HF	Idiopathic DCM	14	63.63%	8	57.14%	6	42.85%	0.054
	Ischemic	7	31.81%	7	100%	0	0%	
	Others(HCM)	1	4.54%	1	100%	0	0%	

STD:Standard deviation, IHD: Ischemic heart disease, HF:Heart failure, DCM:Dilated cardiomyopathy, HCM:Hypertrophic cardiomyopathy

Table 2. Distribution of HF patients according to NYHA Class

NYHA	Pre implant		Post implant	
	No.	%	No.	%
I	0	0%	2	9.09%
II	0	0%	8	36.36%
III	7	31.81%	6	27.27%
IV	15	68.18%	6	27.27%

Table 3. Distribution of HF patients according to ECG criteria

ECG		Pre implant		Post implant		p-value
			%		%	
SR(no.)		18	81.81 %	18	81.81 %	0.91
AF(no.)		4	18.18 %	4	18.18 %	
QRS morphology (no.)	LBBB	20	90.90 %	5	22.72 %	3.66
	RBBB	2	9.09%	3	13.63 %	
	IVCD	0	0%	10	45.45 %	
	Narrow QRS	0	0%	4	18.18 %	
QRS duration(mean)		128 .86		11 5. 71		

SR: Sinus Rhythm, AF: Atrial Fibrillation, LBBB: Left bundle branch block, RBBB: Right bundle branch block. IVCD: Interventricular conduction defect

Table 4. Distribution of HF patients according to Echocardiographic findings

Echo(mean)	Pre implant	Post implant	% of improvement	P-value
LV end-diastolic diameter(mm)	74.59	71	4.82%	**0.18**
EF(%)	27.90	34.22	22.65%	**0.00066**
A-value(mean)	447	412.75	7.66%	**0.14**
B-value(mean)	219.82	216.48	1.5%	**0.79**
Tei index(mean)	1.01	0.86	14.85%	**0.067**
LV end-systolic volume	212.62	188.76	11.22%	**0.29**
SPWMD(mean)	186.4	119.27	36.01%	**0.052**
MR mild/mod./severe (no.)	**8/5/6**	**9/5/4**		

SPWMD: Septal to posterior wall motion delay, MR: Mitral regurgitation

Table 5. ECG & Echocardiographic characteristic between responders & nonresponders.

		Responder		Nonresponder		P-value
			% of change		% of change	
Number		16		6		
ECG	Initial LBBB/RBBB	16/0		4/2		
	QRS width(msec)	110	↓by 14.63%	130	↑by0.88%	**0.18**
Echo	LV end-diastolic diameter(mm)	69.85	↓by 6.35%	73.66	↓by 1.24%	**0.43**
	EF (%)	34.28	↑by 22.86%	33.0	↑by 18.27%	**0.86**
	A-value(mean)	433.23	↓by 3.08%	347.2	↓by 22.32%	**0.003**
	B-value(mean)	224.7	↑by 2.21%	190.2	↓by 13.47%	**0.007**
	Tei index(mean)	0.86	↓by 14.85%	0.87	↓by 13.86%	**0.94**
	LV end-systolic volume(mean)	177.3	↓by 16.61%	231.75	↑by 8.99%	**0.14**
	SPWMD(mean)	108.62	↓by 41.72%	147.66	↓by 20.78%	**0.37**
	MR mild/mod./severe(no.)	8/2/3		1/3/1		
Hospitalization(no.)		**0**		**3**		

EF: Ejection Fraction, SPWMD: Septal to posterior wall motion delay, MR: Mitral regurgitation

DISCUSSION

The principlal findings from this study evaluating the effects of CRT on the Tei index in patients with symptomatic heart failure despite optimal medical treatment include the followings:

There was no age preference in predicting response to CRT (p-value 0.218 between responders and non-responders)

Both sexes show equal response to CRT with no statistically significant difference between them (p-value 0.62). Although MADIT-CRT trial[5] show that the improvement was greatest in females

All ischemic cardiomyopathy show a response to CRT while MADIT-CRT trial[5] reveal that greatest improvement occur in patients with non-ischemic etiology.

And also as noted in MIRACLE study[6], patients with nonischemic cardiomyopathy were more likely to respond to CRT than patients with ischemic cardiomyopathy. The LV Tei index also was lower in patients with ischemic cardiomyopathy, suggesting that they had less remediable dyssynchrony, perhaps related to infarcted nonviable or ischemic myocardium, despite only a borderline difference in QRS duration.[6]

Two of the six patients with DCM who were non responders had RBBB. Another patient had upgrading from pacemaker to CRT and one patient had AF. These reasons together with the small sample size may have resulted in apparently lower response in cardiomyopathy in our study.

72.7% of patients were meeting the criteria of the responders, and 27.3% were non-responders and this is consistent with other trials that show that CRT results in significant improvement of functional and clinical outcomes in the majority of patients. Approximately 70-80% has a response to CRT with 25% show an improvement in HF quality of life scores, distance walked in 6-minute treadmill exercise time, and rate of maximal Oxygen uptake and these benefits are observed regardless of an ischemic or nonischemic cause of HF.[7-11]

All responders 72.72% had an initial LBBB morphology in comparison to just 4 patients (18.18%) of the non-responders(p-value <0.015) while none of the RBBB show a response, revealing that LBBB is strong predictor to response which is consistent with what's mentioned in CARE-HF trial that showed that a baseline typical LBBB pattern predicted a favorable outcome.[12]

A base line rhythm (sinus, AF) had no effect in predicting response (p-0.91), however it is difficult to draw a firm conclusion where only four patients with AF involved in the study.

QRS width decrease by 14.63% in responders while it increases by 0.88% in non-responders reflecting underlying LV synchrony and emphasizing the role of CRT in improving not only interventricular synchronization but also intraventricular synchronization. [13]

LV end-systolic volume, Tei index, and septal to posterior wall motion delay (SPWMD) showed immediate improvement (decrease by 11.22 %, 14.85%, and 36.01% respectively) (after CRT activation) which is sustained with subsequent follow-up.

Ejection fraction (EF) also shows immediate improvement (by 14.85%) and this increment remained sustained after subsequent follow-up.

and this is consistent with a study done by Toshinori et al [14] that reveal that LV volumes (both LV end-diastolic volume [LVEDV] and LV end-systolic volume {LVESV}) decreased significantly in responders (over time, P < .001). LV volume reduction was observed after only 1 day in responders (LVEDV: P < .001, LVESV: P < .001), with additional volume reduction after 6 months (LVEDV: P < .001, LVESV: P < .001 vs baseline and 1-day values). Similarly, LVEF improved significantly in responders (P < .001). LVEF reductions in responders were observed at 1 day (P < .001) and the 6-month follow-up (P<.001 vs baseline and 1-day values).

Also responders had higher mean initial Tei index (1.040) in comparison to non-responders whose their mean initial Tei index was (0.9616) suggesting that the higher Tei index the more it predicts favorable outcome which is consistent with what was reported in Toshinori et al[(15)] study that responders had a higher LV Tei index than nonresponders at baseline. In addition, the baseline LV Tei index was a significant and independent factor associated with LVESV reduction after CRT.[14]

In addition, the change in A value (decrement) post CRT implantation was 7.66% while the change in B value (ejection time) was just 1.5% and this goes with Toshinori et al study that CRT shortens the isovolumic contraction time (ICT) but has a less well- established effect on ejection time (ET) and isovolumic relaxation time (IRT).[(14)]

Although severe mitral regurgitation (MR) decreased in 2 patients only (9.09%) which is statistically non-significant (p value >0.05) this is inconsistent with other trials and a study done by Dragos Vinereanu et al titling (Mechanism of reduction of MR by CRT) revealing that cardiac resynchronization reduces mitral regurgitation by improving LV mechanical synchrony, which leads to an increase in LV longitudinal function and a reduction in subvalvular traction. [16]

CRT results in significant reduction in hospitalization as only 3 patients out of 22 require readmission for HF symptoms which is statistically significant (p-value < 0.0023) which is consistent with COMPANION trial[(17)], that reveal that CRT with or without an ICD, lowered the combined endpoint of all-cause mortality and rehospitalization for HF by 35–40%, mainly driven by the 76% lower rate of hospitalizations[(17)] and CARE-HF

trial[5],that show that CRT-P lowered the proportion of unplanned hospitalizations for worsening HF by 52%, and the number of unplanned hospitalizations for major cardiovascular events by 39%.[18]

Finally it is interesting to know that mechanical dyssynchrony and significant delays in timing of regional contraction among LV segments were not always present in patients with a prolonged QRS interval. This is an important observation and suggests that individuals without significant dyssynchrony (by Echocardiography) may potentially be nonresponders to CRT despite QRS prolongation in ECG.

Conclusion

So in conclusion, this study showed that:

- CRT has been shown to improve the functional status in a majority of patients with drug –refractory Heat failure (ischemic, or dilated cardiomyopathy), and wide QRS complex.
- CRT lowers the rate of Heart failure-related hospitalization in responders.
- Echocardiography can be used to determine the response in LV structure and function after device implantation and emerging as a method for selection of patients who may drive clinical benefits from CRT implantation.

And it is recommended that:

- Prolonged period of observation and follow-up after CRT implantation up to 1 year to assess its effect on regression of MR.
- Inclusion of new Echocardiographic method like Doppler Tissue Imaging (DTI) (that can be used for determination of strain and strain rate) and Tissue Synchronization Imaging for assessment of dyssynchrony before and after CRT.

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