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Effect of cardiac resynchronization therapy on quality of life: Role of hypertension

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Abstract

Aims: *To evaluate cardiac function, quality of life and role of hypertension in symptomatic heart failure in patients with Cardiac Resynchronization Therapy (CRT).*

Methods: *80 patients with heart failure were enrolled in our study. Among them 30 patients underwent CRT implantation (CRT group) and 50 patients received optimal medical therapy only (non-CRT group). Follow-up was carried out for 20 ± 2.828 months. Assessment of New York Hear Association (NYHA) class, QRS width, Ejection Fraction (EF), left ventricular end diastolic diameter, left ventricular end systolic diameter, interventricular septum, posterior wall thickness, degree of Mitral Regurgitation (MR) and Basic Natriuretic Peptide (BNP) level was performed at baseline and follow-up along with number of admissions and Quality of Life (QOL) assessment.*

Results: *The baseline indices of patients in the CRT and non-CRT groups were statistically same (P>0.05). At the end of follow-up most indices showed significant improvement in the CRT group (P<0.05) except thickness of IVS and the PWT (P>0.05). The indices in the non-CRT group only showed significant improvement in EF and BNP level (P<0.05). Hypertensive patients did not show significant impact on number of admissions and QOL (P<0.05).*

Conclusions: *Patients receiving CRT had an overall improved outcome with beneficial effects in cardiac remodeling, enhancing the left ventricular function and improving the quality of life. Hypertension was associated with poorer outcome.*

Keywords: *Heart failure, Ventricular remodeling, Left ventricular function, Cardiac resynchronization therapy, Quality of life.*

Introduction

Congestive Heart Failure (CHF) is associated with significant morbidity and mortality [1]. Despite many advances in management in recent years, heart failure still carries a poor prognosis (30% to 50% mortality rate at 1 year) [1,2].

One of the most important factor for heart failure is hypertension [2]. Left Ventricular (LV) dyssynchrony has been demonstrated by recent studies to be a major contributing factor in such cases which is in turn related to extent of LV hypertrophy and left atrial size [3-6]. Some of the most common risk factors for short and long-term mortality include demographic factors such as older age and male gender [7]; ethnic background (black patients have a higher mortality rate than white patients) [8]; co-morbidities such as diabetes mellitus [9], anemia [10], and poor renal function [11]; and physical examination findings such as a third heart sound and elevated jugular venous pressure [12]. Biochemical markers include elevated aldosterone, angiotensin II, and arginine vasopressin, and elevated Brain Natriuretic Peptide (BNP) [13].

A number of therapeutic strategies have been applied in recent years in the management of chronic heart failure to enhance the quality of life and reduce morbidity and mortality. Treatment options include medications, non-pharmacologic interventions (exercise training, care delivery systems), electrophysiology procedures and devices, and surgery including cardiac transplantation. Cardiac resynchronization therapy is one of the relatively new treatment options for moderate and severe heart failure. CRT involves implantation of device with lead in right atrium, right ventricle and over left ventricle through coronary sinus. CRT aim to improve systolic and diastolic function via cardiac remodeling and decrease in dyssynchrony [14].

In hypertensive patients, stiff hypertrophied myocardium causes abnormal LV relaxation with an elevated LV filling pressure which then leads to diastolic dysfunction and interventricular dyssynchrony. Hence, treatment of hypertension has been shown to have beneficial effect on ventricular dyssynchrony which was attributed to regression in LV hypertrophy and the effect of decrease in blood pressure itself [15].

Our study was conducted with the view to find out the effect of CRT on the outcome of patients who had symptomatic heart failure despite receiving optimal medical therapy both subjectively by analyzing improvement in quality of life and objectively by measuring different parameters of heart remodeling and left ventricular function. The study also aimed to evaluate any effect of hypertension on patients with CRT.

Methods

This study protocol was approved by the ethics committee of Tongji hospital of Tongji University. Informed consent was taken from all subjects included in the study. This study abided by declaration of Helsinki.

Patient selection

The study focused on patients attending cardiology department of our hospital of with chronic symptomatic heart failure irrespective of NYHA class and satisfying the selection criteria. Inclusion criteria included patient's age above 18 years, NYHA class ≥ II heart failure, patients maintained on optimal pharmacological therapy, QRS duration ≥ 120ms, ejection fraction < 35% and Left Ventricular End Diastolic Diameter (LVEDD) ≥ 55mm. The exclusion criteria were based on patients younger than 18 years of age, patients with myocardial infarction during the preceding 30 days, patients who have had previous cardiac resynchronization therapy, life expectancy of less than 6 months due to other medical conditions, patients expected to undergo heart transplant within the next 6 months, pregnant patients and patients who do not satisfy the above mentioned inclusion criteria.

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Patient selection

Electrocardiogram was recorded with 12 Lead ECG machine (Shanghai Hua Tai - China). Triage Meter Plus (Biosite USA) was used for BNP measurement Standard transthoracic echocardiography was done with GE Vivid 7 (USA) echo machine. CRT device (Medtronic InSync III -8042) manufactured by Medtronic (USA) and fluoroscopy apparatus (Siemens Axiom Artis DTA Model 3800351-Germany) were used in our study.

Quality of life assessment was done using Minnesota Living with Heart Failure Questionnaire.

Methods

Baseline assessment

In all, 80 patients satisfying the inclusion criteria were enrolled in our study after giving informed consent. All the patients underwent baseline clinical and investigative assessment.

Patients' NYHA class was based on the history and clinical assessment. A 12 Lead ECG was recorded and the width of QRS complex was kept in consideration. Blood samples were taken at the time of admission for measuring of blood counts and BNP level. Echocardiographic data were obtained according to a standard protocol and echocardiographic measurements and analysis were performed by an experienced examiner. The Echocardiographic indices used for studying left ventricular size and function were: Left Ventricular Ejection Fraction (LVEF), Left Ventricular End-diastolic Diameter (LVEDD), Left Ventricular End-systolic Diameter (LVESD), Thickness of Interventricular septum (IVS), Posterior wall thickness (PWT) and Degree of Mitral Regurgitation (MR).

After baseline investigation, patients were divided in 2 groups. The CRT group (n = 30) included patients who gave consent to undergo the implantation of the CRT device. The patients who did not give consent for CRT implantation were placed in the Non-CRT group or Control group (n = 50). For the purpose of analysis patients in CRT group were subdivided into hypertensive (n = 17) and non-hypertensive (n = 13) groups.

Patients in both the groups were maintained on optimal drug therapy for heart failure which included ACE inhibitors, Beta-blockers, Diuretics and Digoxin if needed.

CRT implantation was done as per standard protocol.

Follow-up

Follow-up was carried out after a year for all patients. Electrocardiography was used to confirm biventricular pacing. The device was completely evaluated for normal functioning parameters. At the follow-up visit, patients were questioned regarding heart failure symptoms and compared with before therapy at baseline. Patient's clinical assessment and objective measures such as ECG (QRS complex), Echocardiography and BNP yielded the required information. Moreover, patients' quality of life and the number of admissions during the study period of CRT patients was also compared to the non-CRT patients.

Statistical analysis

The characteristics of the 2 groups (CRT versus non-CRT) were compared at baseline as well as during follow-up using an unpaired t-test. Paired t-tests were used to assess the within-group differences of the changes in measurements from baseline to the follow-up period and between hypertensive and non-hypertensive groups. Chi-square test was used to assess the gender difference between the two groups of CRT and non-CRT. Multivariate regression analysis was done for prediction of quality of life. The $P < 0.05$ was considered significant for all tests. Statistics data analysis was done with SPSS (version 15.0, SPSS Inc., Chicago, Illinois).

Results

Baseline assessment

The mean age of the CRT group was 73.727 ± 4.429 years and non-CRT group was 72.545 ± 10.318 years ($P = 0.725$). The gender ratio of male to female in the CRT group was 27/3 (90/10 % male/female) while in the NON-CRT group it was 43/7 (86/13% male/female) ($P = 0.737$). The baseline clinical characteristics of CRT group and non-CRT group involved in this study were statistically same (Table 1). A high percentage of patients in both groups used beta blockers (90% CRT vs 86% non-CRT).

Functional parameters were assessed of both CRT and non-CRT groups at baseline and at follow. It showed improvement in left ventricular functional capability except for IVS and PW thickness in CRT group at follow up as compared to Non-CRT group as shown in Table 2. CRT group also showed reduced number of readmissions to hospitals and better quality of life as compared to non-CRT group as evident from Table 3.

As evident from Table 4, hypertensive patients did not show significant improvement in NYHA class. Multivariable regression analysis showed hypertension and NYHA class to be independent predictors of quality of life in CRT patients $P < 0.05$). (Table 5)

Characteristic	*Crt group*	*Control group*
Number of patients	*30*	*50*
Age (years)	*73.72 ± 4.42*	*72.54 ± 10.31*
Gender (m/f)	*27/3 (90/10%)*	*43/7 (86/13%)*
NYHA Class	*2.45 ± 0.52*	*2.6 ± 0.50*
Ejection fraction (%)	*25.72 ± 5.46*	*28.93 ± 4.54*
Left Ventricular End Diastolic Diameter (LVEDD) mm	*68.45 ± 6.77*	*65.06 ± 7.68*
Left Ventricular End Systolic Diameter (LVESD) mm	*57.27 ± 8.05*	*54.86 ± 9.51*
Interventricular septum (mm)	*10.72 ± 1.55*	*10.2 ± 1.52*
Posterior wall thickness (mm)	*10.36 ± 1.56*	*9.33 ± 1.29*
Degree of MR	*2.181 ± 0.404*	*1.8 ± 0.676*
BNP (pg/ml)	*1308.45 ± 622.84*	*1716.66 ± 975.47*
QRS width (ms)	*142.72 ± 12.72*	*134 ± 12.42*
Diabetes	*11/30 (36.6%)*	*16/50 (32%)*
Hypertension	*17/30 (56.6%)*	*30/50 (60%)*
Coronary artery disease	*27/30 (90%)*	*43/50 (86%)*
Arrythmias	*6/30 (20%)*	*10/50 (20%)*
Hyperlipedemia	*8/30 (26.6%)*	*17/50 (34%)*
Renal failure	*1/30 (3.3%)*	*3/50 (6%)*
Beta blocker	*27/30 (90%)*	*43/50 (86%)*
ACEI	*19/30 (63.3%)*	*33/50 (66%)*
Nitrates	*17/30 (56.6%)*	*29/50 (58%)*
Digoxin	*18/30 (60%)*	*28/50 (56%)*
Diuretics	*19/30 (63.3%)*	*30/50 (60%)*
Lipid lowering agents	*18/30 (60%)*	*31/50 (62%)*

Table 1. *Baseline characteristics of CRT and NON-CRT groups.*

Functional Parameter	Baseline	Follow Up	P value
NYHA class:			
CRT group	2.45 ± 0.52	1.81 ± 0.60	0.01
NON-CRT group	2.6 ± 0.507	2.466 ± 0.516	0.77
QRS width:			
CRT group	142.72 ± 12.72	124.54 ± 14.39	0.01
NON-CRT group	134 ± 12.42	135.33 ± 11.87	0.54
Ejection fraction:			
CRT group	25.72 ± 5.46	39.45 ± 8.09	0
NON-CRT group	28.93 ± 4.54	32.2 ± 9.13	0.02
Left ventricular end diastolic diameter (LVEDD in mm)			
CRT group	68.45 ± 6.77	62.90 ± 6.22	0.01
NON-CRT group	65.06 ± 7.68	68.26 ± 6.05	0.06
Left Ventricular End Systolic Diameter (LVESD in mm)			
CRT group	57.27 ± 6.22	53.09 ± 5.76	0.01
NON-CRT group	54.86 ± 9.51	59.8 ± 5.44	0.37
Interventricular Septum thickness (IVS in mm).			
CRT group	10.72 ± 1.55	10.54 ± 1.43	0.44
NON-CRT group	10.2 ± 1.52	10.66 ± 1.75	0.26
Posterior Wall Thickness (PW in mm)			
CRT group	10.36 ± 1.56	10.09 ± 1.30	0.19
NON-CRT group	9.33 ± 1.29	9.533 ± 1.68	0.38
Degree of Mitral Regurgitation			
CRT group	2.18 ± 0.40	1.45 ± 0.52	0
NON-CRT group	1.8 ± 0.67	2.07 ± 0.61	0.16
BNP level (pg/ml)			
CRT group	1308.5 ± 622.8	610.4 ± 298.1	0.01
NON-CRT group	1716.7 ± 975.5	1112.5 ± 708.8	0.01

Table 2. *Functional Parameters of CRT and NON-CRT group at baseline and follow up.*

	CRT	NON-CRT	P Value
Average No. of Admissions	1.63 ± 2.06	3.63 ± 2.24	0.04
Average Quality of Life	48.63 ± 3.88	52.72 ± 4.33	0.03

Table 3. *Comparison of Number of admissions and quality of life in CRT and NON-CRT groups during study period.*

Discussion

SThere has been focused update about improved clinical outcome in NYHA III/IV patients with CRT therapy in PROSPECT TRIAL [16]. We included all the patients of heart failure with symptoms regardless of their NYHA class and evaluated not only the objective parameters of heart failure including ejection fraction, LVED dimensions, LVES dimensions, degree of MR jet, blood levels of BNP but also focused our attention to subjective improvement.

We determined the general well-being of the patient and their quality of life through Minnesota Living with Heart Failure Questionnaire. Because knaclestedt C, et al. [17] found that psychological depression symptoms persist after CRT-D therapy. It becomes very important to evaluate patients both subjectively and objectively after CRT therapy. What the source of bias in knaclestedt C, et al. study was that they included the patients with advanced heart failure regardless of control selection for comparison. What Lenarczyk R, et al. [18] determined was that those who do not improve with CRT therapy have 2.7 times increased probability of future major adverse cardiovascular events (MACEs) therefore explaining the bias encountered in knaclestedt C study. Badalek MK, et al. [19] rightly demonstrated improvement in 6-minute walk time and psychological general wellbeing index after CRT therapy in heart failure patients. The results of our study show that CRT therapy improves cardiac remodeling and left ventricular functional parameters in symptomatic heart failure regardless of NYHA class and has a positive impact in improving the quality of life.

Index	Baseline	Follow Up	P value
NYHA class:			
HTN group[a]	2.35 ± 0.43	2.15 ± 0.51	0.61
NON-HTN group[b]	2.55 ± 0.41	1.51 ± 0.44	0.01
QRS width:			
HTN group	144.28 ± 11.63	126.35 ± 12.93	0.03
NON-HTN group	140 ± 10.38	121.73 ± 10.76	0.01
Ejection fraction:			
HTN group	23.41 ± 5.37	35.47 ± 7.01	0.04
NON-HTN group	28.54 ± 4.48	43.15 ± 8.06	0.03
Average No. of admissions	2.26 ± 3.56		
HTN group	1.15 ± 6.55		0.03
NON-HTN group			
Average Quality of Life	40.35 ± 5.13		
HTN group	55.79 ± 6.42		0.03
NON-HTN group			

[a]Hypertensive and [b]Non-Hypertensive groups

Table 4. *Indices of Hypertensive and Non-hypertensive patients in CRT group.*

	Multivariable analysis	
	HR (95% CI)	P value
Age	1.01 (1.05-1.08)	0.31
Gender	1.15 (0.94-1.51)	0.25
Hypertension	1.49 (1.09-1.99)	0.01
Diabetes	1.17 (0.93-1.55)	0.27
Smoking	1.03 (0.82-1.35)	0.81
BMI	0.97 (0.78-1.34)	0.79
Ejection Fraction (Baseline)	0.81 (0.63-1.07)	0.16
QRS width	1.16 (0.79-1.69)	0.32
NYHA Class	1.27 (1.11-1.70)	0.03
BNP	0.91 (0.74-1.43)	0.68

Table 5. *Multivariable Regression Analysis for Predictors of Quality of Life (QOL) in CRT patients.*

Left ventricular remodeling

Our study measured the benefits of CRT pacing as compared to optimal medical therapy for symptomatic heart failure. Despite having features of cardiac and systemic diseases, CRT group showed a reduction in ventricular size, as evidenced by a highly statistically significant reduction in LV dimensions and was associated with a trend toward a greater reduction in ventricular size.

Chronic heart failure patients in this study showed signs of positive cardiac remodeling. Patients of heart failure included in studies like MIRACLE and MIRACLE ICD studies also had comparable results. In these 2 studies, significant reverse remodeling and improvement in LVEF were seen in heart failure patients receiving CRT [20].

QRS complex: Prior studies demonstrated a good relation between interventricular dyssynchrony and the QRS duration. These observations tend to support the use of the QRS duration for patient selection. However, results of many CRT studies indicated that 20-30% of the patients failed to respond to CRT, despite a prolonged QRS duration. Except for patients with a very wide spontaneous QRS complex, mechanical intraventricular dyssynchrony is not necessarily related to electrical dyssynchrony judged by the QRS duration. This, among other factors, may at least in part explain why 20-30% of the patients in major trials did not respond to CRT [21].

The fact that, in our study we selected patients with QRS duration of ≥ 120 ms and hence with more ventricular dyssynchrony may have led to a more favorable response to LV pacing. As evidenced by Table 2, CRT decreased the QRS duration in 90% of CRT patients. About 10% did not respond to CRT therapy. In comparison only 26% of non-CRT patients showed improvement in QRS width while 74% either remained static or did not improve.

Left ventricular dimensions: Resynchronization therapy is chronically changing the contractile response of the ventricle [22]. LVESD and LVEDD improved in CRT whereas non-CRT group did not show improvement (Table 2). Potential mechanisms responsible for reductions in LV end-systolic diameter in CRT group include CRT-induced improvement in contractile response or decreased systemic vascular resistance [20,22].

Mitral regurgitation: A major benefit of reverse remodeling was the reduction in severity of MR, which did not occur in the control group. As seen in Table 2, degree of MR in CRT group reduced (P = 0.001) while the non-CRT group did not show any significant reduction (P = 0.164).

MR in patients with LV dysfunction is a powerful risk factor for poor clinical outcome [23]. In chronic congestive heart failure, MR results in further LV dilatation, thus escalating the onset of hemodynamic decompensation and exacerbating LV dysfunction. In this study, the factors leading to the improvement in MR probably were the decrease in LVESD, coordination of ventricular contraction and improved atrioventricular coupling that ultimately restored mitral subvalvular size and function toward normal.

Left ventricular function

NYHA class: Our study showed that CRT has positive effect on the NYHA class of heart failure patients (Table 2). CRT group patients in general showed improvement in their NYHA class as compared to the non-CRT group which more or less remained static with a slight trend towards the negative side. This fact can also be judged by comparing the number of admissions of both the groups during the study period. Patients with CRT on average showed less number of admissions as compared to the control group.

Left ventricular ejection fraction: A key finding in this clinical study was the significant increase in LVEF seen during follow-up. The results from our study showed a great improvement in LVEF (Table 2) in both the CRT and non-CRT groups. (P = 0.009 and 0.025 respectively).

LV dyssynchrony is an important factor contributing to decreased ejection fraction and is associated with poor outcomes due to abnormal remodeling. Hypertension contributes to such a scenario in terms of increased left atrial size, LV hypertrophy and increased LV filling pressure [24]. Our study complimented such results showing greater dyssynchrony in patients with hypertension.

A high number of patients used beta-blockers in our study (> 90% of patients) as compared with 58% in the MIRACLE study [25], 28% in the Multisite Stimulation in Cardiomyopathy (MUSTIC) trial [26], and 67% in the more recent Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial [27]. However, the stabilization of doses of ß-blockers and angiotensin-converting enzyme inhibitors for at least 60 days before randomization should have minimized the contribution of medical therapy to the echocardiographic changes.

BNP: It is one of the most important parameters in assessment of cardiac function. BNP is a useful marker for the diagnosis and prognosis of HF and may be helpful to guide medical management. Rising BNP level is associated with an increased risk of cardiac events and death in patients with chronic HF. Several previous studies reported a significant decrease in natriuretic peptide following CRT implantation. Fruhwald, et al. [28] demonstrated, in patients with moderate or severe HF and LV dyssynchrony, that CRT exerts an early and sustained reduction in BNP reflecting the improvements in LV geometry and function. Moreover, the Care-HF post-hoc analysis concluded that BNP may be used to monitor CRT effect. Consistently, Kubanek, et al. [29] found similar results and reported that a decrease in BNP>6.7% between baseline and 3 months follow-up is accurate to differentiate responders from non-responders patients (specificity = 77% and sensibility = 90%). Patients in our study also showed significant decrease in their BNP level (Table 2). The improved BNP seen in patients receiving CRT suggests that CRT may have a favorable effect on the prognosis of patients with symptomatic advanced heart failure.

Number of admissions: As seen from Table 3, during study period the number of admissions in the CRT group were significantly less than the number of admissions in the non-CRT group (P = 0.048). This may be attributed the combined beneficial effects of CRT on cardiac structure and function which ultimately led to a decrease in morbidity. A study by Penicka M [30] also shows that CRT is beneficial in decreasing hospitalizations in this very ill population of NYHA class IV patients.

Quality of life: The assessment of quality of life was based on the Minnesota Living with Heart Failure Questionnaire. The results of the current study highlight important aspects of CRT and suggest that CRT in comparison to non-CRT group (P = 0.030) improves general health-related quality of life, particularly in the domains of physical functioning and feelings of vitality. This can be attributed to role of hypertension in such patients as hypertensive patients did not show much improvement in quality of life which may in turn be due to persistent asynchrony.

Limitations of study

The sample was relatively small and we believe that the results could have been more representative if a large sample was available. One of the reasons for the relatively small sample was the cost of CRT implantation. Currently CRT's high cost limits its use which sometimes leads to deprivation of deserving patients from receiving the therapy.

Conclusion

CRT causes cardiac remodeling and improves left ventricular functional parameters in symptomatic heart failure patients. It improves quality of life by improving both physical health and mental vitality according to modified Minnesota quality of life heart failure questionnaire. Hypertension is one factor which can affect the quality of life in CRT patients. As it is a modifiable factor, better control of blood pressure may result in better response to CRT. Further studies are warranted to further evaluate the role of hypertension and its control.

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