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RESEARCH ARTICLE

ELECTROCARDIOGRAPHIC PREDICTORS OF CLINICAL RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITH HEART FAILURE

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ABSTRACT

Cardiac resynchronization therapy (CRT) is one of the established treatment modalities for systolic heart failure with wide QRS morphology on electrocardiogram (ECG). It acts by synchronized pacing of left and right ventricles in order to coordinate systolic contraction of the left ventricular septum and the free wall. Predicting proper responders to the CRT still remains elusive. Post-implantation 12-lead ECG showing a tall R wave in lead V_1 of ≥4 mm and predominant negative deflection (S wave) in lead I (RV_1S_I pattern) has been postulated as a marker of optimal resynchronization after CRT. We investigated whether presence of this ECG pattern predicts better response and improvement in heart failure outcomes at 6 months after CRT device implantation and found to be very much helpful. **Method**: Post-implant 12-lead ECG of 75 patients were reviewed and divided into two groups based on the positive RV_1S_I (Group I) or negative RV_1S_I (Group II) pattern on ECG. At six months, follow-up response rate was assessed on the basis of echocardiographic parameters of Left Ventricular End Systolic Volume (LVESV) & Left Ventricular Ejection Fraction (LVEF), and functional assessments {(Packer's Clinical Composite Score, 6-minutes walk test (6MWT) and Minnesota living with heart failure questionnaire (MLWHF)} compared to baseline (pre-implant) values. **Result**: Evaluation of the post-CRT ECG of 75 patients revealed 29 (38.66%) in Group I and 46 (61.33%) in Group II. It was found that patients in Group I showed better response to CRT in comparison to Group II with respect to improvement in echocardiographic parameters (LVESV reduction of 25.69% vs. 21.81% and EF improvement of 40.29% vs. 33.44%) and functional assessment parameters (6MWT improvement 374.6 meters vs. 218.06 meters, MLWHF improvement 3.85 vs. 1.22 and clinical composite score (New York Heart Association functional class improvement from class IV to II 75% vs. 50% and heart failure related hospitalization after CRT implantation of 3.45% vs. 21.74%). **Conclusion**: Patients with a positive RV_1S_I pattern in post-implant 12-lead ECG showed better response with CRT at six months. This simple tool can be used to predict clinical improvement after therapy and accordingly proper positioning of the LV lead or programming the lead-vectors to get such ECG pattern may yield proper CRT response.

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INTRODUCTION

Heart failure (HF) is one of the major public health problems worldwide. CRT is one of the established treatment options for patients with HF with reduced left ventricular ejection fraction and wide QRS morphology in surface ECG. It has proven benefit over dual chamber implantable cardiac defibrillator or medical therapy alone (Bardy, 2005; Moss, 2009). CRT provides beneficial effects by several mechanisms, and the most important of them is by synchronizing left ventricular contraction in patients who have dyssynchrony and by pacing both left and right ventricles to coordinate systolic motion of the left ventricular septum and free wall.

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CRT implantation is a class I indication according to the recent guidelines in HF with left bundle branch block (LBBB) having New York heart Association (NYHA) class II –IV (ambulatory) symptoms, and QRS duration greater than 150 msec (Yancy *et al.*, 2013). It has been shown in many studies that 30% to 40% of HF patient do not show clinical improvement after implantation of CRT (non-responder) (Chung *et al.*, 2008). The explanations for this includes insufficient pre-implant left ventricular mechanical dyssynchrony and excess left ventricular scarring. So it is important to identify those variables, which correlate with poor long-term outcomes after CRT implantation. Many pre-implantation variables such as clinical classifications, ECG parameters and imaging have been identified that can correlate with clinical outcomes (Boidol, 2013; Ellims, 2013; Brenyo, 2011). Some studies have shown different post-implantation parameters to predict clinical response after implantation (Sweeney, 2010). Post-implantation ECG is one of the important tools that can predict response to CRT and can help in proper programming. Post-implantation Bi-ventricular pacing results in QRS complexes, which represents fusion of the wave fronts initiated from the right ventricular lead and left ventricular leads. Successful Bi-ventricular pacing should result in QRS vector directed anteriorly, rightward and superiorly. This typically will produce prominent R waves in lead V_1, V_2, and aVR; qS waves in lead I and aVL; and a northwest axis (Barold, 2011; Barold, 2011; Giudici, 2007). This pattern may be simplified to a predominant negative deflection (S wave or qS) in lead I and R wave greater than or equal to 4 mm in V_1, which we describe as an RV_1S_I pattern. Absence of this pattern may be due to suboptimal lead placement, improper timing of ventricular pacing and masked conduction abnormality from pacing site (Bleeker, 2006).

Few studies are available in which presence of RV_1S_I in post-CRT implantation ECG was used as predictor of clinical response. These studies were performed as retrospective observational cohort study and therefore may have limitation in reliability for long-term follow-up. The outcome in these studies were analysed by cardiac death or hospitalization only and they had not assessed functional improvement in Quality of life (QoL) and symptomatic improvement by objective means (i.e. 6 minute walk test) and echocardiographic improvement by analysing LVEF and LVESV. This study was conducted to see whether post-implantation ECG having RV_1S_I pattern could be used as a predictor of outcomes in patients of heart failure after CRT implantation.

MATERIALS AND METHODS

The study was a prospective, observational study conducted in the Department of Cardiology, PGIMER & Dr. Ram Manohar Lohia Hospital, New Delhi after the approval of ethical committee. Consecutive 75 patients presenting to our hospital with heart failure from August 2015 to December 2017, who underwent indicated CRT implantation as part of their therapy, were included in the study. All patients of HF with age more than 18 years, LVEF ≤35%, LBBB morphology in surface ECG with QRS duration of more than 150 msec, NYHA class II–IV (ambulatory) were included in the study. Patients with change in follow-up ECG pattern from post-implant ECG pattern, or biventricular pacing of less than 90% were excluded from the analysis. A detailed history regarding symptom class as per NYHA functional classification, and cardiac co-morbidities like coronary artery disease (CAD), hypertension, diabetes, were noted and physical examination findings were recorded. Patients were divided in two groups, Group I & Group II, based on positive or negative RV_1S_I pattern on post-implantation ECG. These two groups were compared in the follow-up on the basis of echocardiographic parameters (LVESV reduction percentage and LVEF% improvement), functional assessment (Packer's Clinical Composite Score, NYHA Class changes, 6-minutes walk test (6MWT) and rate of rehospitalisation for heart failure & mortality. Measurement of QRS duration, QRS axis, S wave in Lead I, height of R wave in chest lead V_1 were done according to the published literatures (Barold, 2011; Barold, 2011; Giudici, 2007). Coronary angiography was done according to the departmental protocol with very low amount of iodinated iso-osmolar contrast agents to visualize coronary arteries & coronary venous anatomy in levophase**.** CRT device was placed by standard technique with left ventricular (LV) lead in suitable coronary vein. A quadripolar LV lead was used in most (95%) of the cases and a bipolar LV lead was used in the remaining cases to pace the left ventricle. Pharmacotherapy of patients was optimized as per guideline based medical therapy (Yancy *et al*., 2013). Patients were followed up in the pacemaker & device clinic of the department as per protocol at 15 days, 3 months and 6 months post CRT implantation. 2D Echocardiography, MLHFQ, and 6MWT were done at each of those follow-up visits. Outcome was assessed at each follow-up visit by assessing objective symptom improvement by 6MWT (Pollentier, 2010), clinical composite score assessment by NYHA class, hospitalization due to decompensated HF, Quality of life (QoL) assessment by MLHFQ (Rector, 1992), all-cause mortality, and improvement in LVEF and LVESV by 2-D echocardiography. Responders were those who showed >10% improvement in MLHFQ, > 10% increase of the 6-minutes walk distance, >15% absolute reduction in LVESV and/or >10% improvement in LVEF from baseline.

Statistical Analysis: Categorical variables were presented in number and percentage and continuous variables were presented as mean ± SD and median. Quantitative variables were compared using unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-Square test /Fisher's exact test. Diagnostic test was used to find out sensitivity, specificity, NPV and PPV. Univariate logistic regression was used to find out the significant risk factors affecting the outcome. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

A total of 75 patients who fulfilled the inclusion criteria were included in the study. There was no significant difference in baseline characteristics with respect to ECG, Echocardiographic parameters, 6MWT, and MLHFQ in patients of both the groups as shown in table 1. The mean age of the patients was 57.63 ± 8.39 years and 46 (61.33%) of them were male. Out of the 75 patients, 29 (38.67%) were in Group I and 46 (61.33%) were in Group II. Comparison of baseline and six-month changes in echocardiographic parameter and functional assessment between Group I and Group II are shown in table 2 and 3 respectively which suggests better changes in Group I as compared to Group II. Out of 46 patients in Group II, 30 (65.22%) were responders and out of 29 patients in Group I, 26 (89.66%) were responders (p = 0.028). We also found that rehospitalisation rate (table 4) was significantly higher in Group II as compared to Group I (21.74% vs. 3.45%, p = 0.042).

DISCUSSION

This study was a prospective, observational study conducted in a tertiary care hospital. Patients were followed up regularly according to the protocol of the institution and final evaluation of studied parameters was done at six months after CRT implantation. We found that out of the total 75 patients, 29 (38.67%) were in Group I and 46 (61.33%) were in Group II. Out of the 46 patients in Group II, 30 (65.22%) were responders and out of the 29 patients in Group I, 26 (89.66%) were responders (p = 0.028). We also observed that rehospitalisation was significantly higher in Group II as compared to Group I (21.74% vs. 3.45%, p = 0.042).

Table 1. Baseline characteristics of the heart failure patients' in Group I and Group II.

Characteristics		Group I (n=29)	Group II(n=46)	*p*-value
Mean Age		57.97 ± 9.54	57.41 ± 7.68	0.957
	Male	18 (62.07%)	28 (60.87%)	0.971
Sex	Female	11 (37.93%)	18 (39.13%)	0.971
QRS duration (Pre) Mean (Sec.)		155.86 ± 11.81	151.52 ± 10.74	0.108
LVESV(Pre) Mean		158.48 ± 34.72	157.85 ± 23.53	0.931
LVEF (Pre) Mean		26.03 ± 3.63	25.98 ± 3.89	0.934
6MWT (Pre) Mean distance (meter)		293.9 ± 68.63	297.96 ± 67.96	0.861
MLHFQ (Pre) Mean		61.55 ± 8.04	62.54 ± 8.87	0.406
Dilated cardiomyopathy		20 (68.97%)	25 (54.35%)	0.208
Ischemic cardiomyopathy		9 (31.03%)	21 (45.65%)	0.208

Abbreviations: LVESV- left ventricular end-systolic volume, LVEF- left ventricular ejection fraction, 6MWT-6-minutes walk test, MLHFQ- Minnesota living with heart failure questionnaire.

Table 2. Comparison of baseline and 6 months changes in echocardiographic and clinical parameters between Group I and II.

	Group I (n=29)	Group II (n=46)	*p*-value
LVESV (Baseline)			
Mean ± SD	158.48 ± 34.72	157.85 ± 23.53	
Median	156	156	0.931
Inter quartile Range	142 - 174	121.500 – 192	
LVESV (6 month)			
Mean ± SD	117.76 ± 34.74	123.41 ± 31.83	
Median	110	120.5	0.381
Inter quartile Range	81.750 - 143	96 - 150	
LVEF (Baseline)			
Mean ± SD	26.03 ± 3.63	25.98 ± 3.89	
Median	25	25	0.934
Inter quartile Range	25 - 30	25 - 30	
LVEF (6 month)			
Mean ± SD	36.52 ± 4.12	34.67 ± 6.14	
Median	38	35	0.341
Inter quartile Range	35 - 40	30 - 40	
6MWT (Baseline) distance (meter)			
Mean ± SD	65.4 ± 51.3	97.96 ± 67.96	
Median	75	316.5	0.861
Inter quartile Range	-24-179	252 - 342	
6MWT (6 month) distance (meter)			
Mean ± SD	440 ± 87.36	416.02 ± 124.9	
Median	462	415.5	0.332
Inter quartile Range	390 - 496.500	330 - 522	
MLHFQ (Baseline)			
Mean ± SD	61.55 ± 8.04	62.54 ± 8.87	
Median	63	64	0.406
Inter quartile Range	57.500 - 65.750	58 - 70	
MLHFQ (6 month)			
Mean ± SD	65.4 ± 51.3	63.76 ± 10.46	
Median	36	30	0.29
Inter quartile Range	26 - 43	27.750 - 40	

Abbreviations: LVESV- left ventricular end-systolic volume, LVEF- left ventricular ejection fraction, 6MWT- 6-minutes walk test, MLHFQ- Minnesota living with heart failure questionnaire.

Table 3. Change in NYHA functional class, mean of echocardiographic parameters, and functional assessment parameters at six month follow up in Group I and II

Parameters	Group I (n=29)	Group II (n=46)
NYHA Class (Baseline)	Class III- IV (29) 100%	Class III- IV (46)100%
NYHA Class (6 Months)	Class II (22) 75%	Class II (23) 50%
LVESV Reduction	25.69%	21.81%
LVEF Improvement	40.29%	33.44%
6 MWT Distance (m)	374.6	218.06
MLHFQ Improvement	3.85	1.22
NYHA improvement (IV to II)	75%	50%

Abbreviations: NYHA- New York Heart Association, LVESV- left ventricular end-systolic volume, LVEF- left ventricular ejection fraction, 6MWT- 6-minutes walk test, MLHFQ- Minnesota living with heart failure questionnaire.

Table 4. Response to CRT and rate of rehospitalisation at six months in Group I and II

Parameters	Group I (n=29)	Group II (n=46)	Total (n=75)	*p*-value
Non -responder	3 (10.34%)	16 (34.78%)	19 (25.33%)	
Responder	26 (89.66%)	30 (65.22%)	56 (74.67%)	0.028
No rehospitalisation	28 (96.55%)	36 (78.26%)	64 (85.33%)	
Rehospitalisation	1 (3.45%)	10 (21.74%)	11 (14.67%)	0.042

It was noted that presence of RV_1S_I pattern on post-implantation surface ECG was a good predictor of clinical response to CRT therapy at a short follow-up period of six months. Similar result was found in a study done by E. Cover stone and collegues (Coverstone, 2015) in which they reviewed the post-CRT ECG of 213 patients and used RV_1S_I pattern as a predictor of clinical response to CRT therapy at 1 year. This study was retrospective in nature and the outcome was a combination of all-cause mortality, unplanned hospitalization, and advanced heart failure therapy at 1 year follow-up. They found that 26.3% of patients exhibited the RV_1S_I pattern as compared to 38.67% in our study. These patients had significantly less chance to achieve the primary end point as compared to patients without the RV_1S_I pattern (33.9% vs. 52.2%; Log Rank $p = 0.022$). This difference was mainly driven by less unplanned hospitalization in these patients. The predictive value remained significant after adjustment for potential confounders ($p = 0.004$).

In our study we found that R wave in $V_1 \geq 4$ mm and S wave in lead I was associated with better outcome after CRT implantation. Similar result was found in a study by Sweeney and collegues (Sweeney *et al*., 2010) in which they analysed the pre- and post-implantation ECG of 202 patients who underwent CRT placement with underlying LBBB. Positive response was defined by >10% reduction in LV end-systolic volumes. In this study 45.5% patient met the end point. The multivariate regression analysis showed increasing R-wave height in V_1 and V_2 (in our study we used R wave in $V_1 \geq 4$ mm) as well as a shift from left-axis deviation to right-axis deviation were associated with echocardiographic response to CRT. These findings coincide with the clinical association of the RV_1S_I pattern with hard clinical end points. Barold *et al.* (2011) in their study described the typical ECG of biventricular pacing with a dominant R wave in V_1 and the presence of right axis deviation which was associated with optimal CRT pacing. In our study we found that the duration of the paced QRS did not correlate with the HF outcomes, similar results were reported by other investigators also (Coverstone, 2015; Tereshchenko, 2011).

In our study we found that the mean percent decrease in LVESV in responders at 6 month was 29.94% (SD = 8.24). Decrease in LVESV significantly correlates with positive outcome. Previously LVESV was assessed in PROSPECT study sub-analysis (Van Bommel, 2009), in which response to CRT was assessed by clinical composite score and LV end systolic volume (LVESV) reduction of >15% at 6-month follow-up. Reduction in LVESV (i.e. LV reverse remodelling) was demonstrated to correlate with survival in HF trials with medical treatment (Kenchaiah, 2004) as well as after CRT (Yu, 2005; Ypenburg *et al*., 2009). Relation between the extent of LVESV reduction and long-term clinical outcome was determined by Yu *et al*. (2005). They reported that patients with >10% reduction in LVESV after CRT had significantly better survival compared with patients with <10% reduction in LVESV. In our study we found that there was significant improvement in mean 6MWT distance at 6 months in Group I as compared to Group II. Similar result was found in a study done by Marıa Angeles Castel *et al*. (2009) in which 188 consecutive post-CRT implant patients were evaluated and they found absolute improvement in 6MWT distance of 117 meters at 6 month follow-up. They also found that 6MWT distance less than 225 meters (HR 5.6 (95% CI: 1.2–25.3) $p = 0.026$) was an independent predictor of cardiovascular mortality. There was significant improvement in NYHA class assessment from class IV to class II in Group I as compared to Group II (75% vs. 50%). In our study at 6 month follow up it was observed that there was significant improvement in mean MLHFQ score in group I as compared to group II. Similar result was reported in a study by Dixit *et al*. (2010) where they found a significant improvement in MLHFQ at 3 months after CRT implantation. The poor response to CRT even among candidates having maximum pre-implant features of good response may result from both modifiable and non-modifiable clinical and pacing-related parameters. One of the most important factors is suboptimal left ventricular lead placement, which can happen if enough importance is not given in selecting the site of LV pacing. Therefore, utilization of an ECG pattern at the time of implantation that correlates with better clinical outcomes not only has utility in future risk reduction, but can significantly reduce the non-responders.

Conclusions

The presence of RV_1S_I pattern in post CRT implantation surface ECG is a predictor of better clinical response and less re-hospitalisation in patients with HF at 6 months after CRT implantation. This simple tool can be used to predict clinical outcomes and risk stratify patients after CRT implantation. Although this alone may not always be sufficient to predict responders, but may help in finding out the responders along with all other means. RV1SI pattern may be used as a guide to place the LV lead in proper coronary sinus tributary or immediately after implantation to program lead vectors to yield such an ECG pattern for better outcome.

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