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Left Axis Deviation: A Sign of Poor Prognosis in Patients with Cardiac Resynchronization Therapy

Mohammad Hossein Nikoo [1, *], Mohammad Vahid Jorat [1], Amir Aslani [1], Sara Barzegar [1], Milad Anvaree [1]

[1] Cardiovascular Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran

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ABSTRACT

Background: Cardiac Resynchronization Therapy (CRT) is one of the suggested managements in patients with Left Bundle Branch Block (LBBB) and heart failure with reduced ejection fraction. Finding a predictor for poor response to CRT may help better candidate selection for device implantation and better final outcome.

Objective: This retrospective study aimed to assess QRS left axis deviation as a novel indicator of clinical and echocardiographic response to CRT.

Methods: This retrospective single-center analysis was done on 95 CRT patients with LBBB in their electrocardiograms (47 patients had normal QRS axis and 48 had left QRS axis deviation). These patients were followed up for 19 ± 3 months after CRT implantation. Response to CRT was evaluated by assessment of New York Heart Association (NYHA) functional class, echocardiographic examination, and number of hospitalizations within six months before and after CRT implantation.

Results: The response rate to resynchronization was 65.9% in the left axis group and 77.3% in the normal axis group, and the difference was statistically significant (P = 0.013). Improvement in echocardiographic findings, including increase in the left ventricular ejection fraction (P = 0.004), decrease in the end diastolic volume (P = 0.010), and decrease in the end systolic volume (P = 0.014), were also noted. However, improvement in NYHA class was reported in both groups without any statistically significant difference (P = 0.066).

Conclusion: Left axis deviation was associated with a lower rate of CRT response in patients with CRT implantation and LBBB.

1. Background

Heart failure is the leading cause of death among patients with cardiac disease (1), especially after improvement in other areas of cardiovascular diseases like coronary artery disease and arrhythmia (2). In addition, a higher mortality rate than other malignancies has been reported without proper management (3). Even with timely medical treatment, a great percentage of patients suffer from malignant complications, such as cardiac arrest and cardiogenic shock, and do not experience an acceptable quality of life due to dyspnea and inability to work adequately (4). Implantation of Cardiac Resynchronization Therapy (CRT) is an acceptable and effective management if proper patient selection is performed (5). CRT seems to be suitable for one-third of the patients who are refractory to medications and have wide QRS complexes with low ejection fraction (6, 7). CRT refers to the insertion of electrodes in the left and right ventricles of the heart, as well as on occasion the right atrium, to treat heart failure by coordinating the functions of the left and right ventricles via a pacemaker (a small device inserted into the interior chest wall). CRT is indicated in patients suffering from a low ejection fraction (typically < 35%), indicating heart failure where electrical activity has been compromised with prolonged QRS duration to > 120 ms (6, 8). The insertion of electrodes into the ventricles is done under local anesthesia with access to the ventricles most commonly via the subclavian vein although access may be conferred from the axillary or cephalic veins. Right Ventricular (RV) access is direct, while Left Ventricular (LV) access is conferred via the Coronary Sinus (CS). CRT defibrillators (CRT-D) also incorporate the additional

Corresponding author: Mohammad Hossein Nikoo, Cardiovascular Research Center, Mohammad Rasoul-allah Research Tower, Mollasadra Street, Shiraz, Iran, Tel: +98-7136122238, E-mail: mhnmp@yahoo.com.

function of an Implantable Cardioverter Defibrillator (ICD) to quickly terminate an abnormally fast life-threatening heart rhythm (9). CRT and CRT-D have become increasingly important therapeutic options for patients with moderate and severe heart failure (6).

CRT with pacemaker only is often termed 'CRT-P' to help distinguish it from CRT-D. CRT requires the placement of an electrical device for biventricular pacing along with placement of (at least) two pacing leads to facilitate stable LV and RV pacing. For all elements, the first stage of the process involves local anesthesia followed by incision to allow for approach from the appropriate vein where the leads and the device can be inserted. Although doubtful blames have continued for years, recent studies have proved that resynchronization improves survival and quality of life and decreases arrhythmic events following a short period of time after CRT implantation (6, 10). Interestingly, this is the only therapy that increases the efficiency of the cardiac muscle without any further energy consumption (11). However, like other modalities, overuse is prevalent among electrophysiologists and, consequently, finding the best responders is a hot topic among researchers (12).

2. Objectives

The present retrospective study aimed to assess QRS left axis deviation as a novel indicator of clinical and echocardiographic response to CRT (13).

3. Patients and Methods

3.1. Study Population

In this study, CRT patients were evaluated in the cardiology clinics affiliated to Shiraz University of Medical Sciences from 2012 to 2014. The patients' demographic data, including age, sex, previous cardiac history, New York Heart Association (NYHA) functional class, and previous medical and drug history, were gathered from their medical records. Patients with available 12-lead ECGs before CRT implantation and available comprehensive echocardiographic studies (performed by an expert echocardiographer) were enrolled into the study. NYHA functional class was recorded from pre-operation notes as well as from our registry follow-up notes. History of admissions within six months before and after the procedure was also recorded from the medical records.

3.2. Patient Selection for CRT Implantation

The inclusion criteria of the study were Left Ventricular Ejection Fraction (LVEF) ≤ 35%, QRS duration ≥ 130 msec, sinus rhythm, Left Bundle Branch Block (LBBB) QRS configuration, NYHA class ≥ II, and showing no clinical improvement despite using maximum tolerable drugs for heart failure according to the current guideline.

3.3. CRT Implantation Procedure

A venipuncture was made and a guide wire was inserted into the vein where it was guided through to the right ventricle using real time X-ray imaging. The guide wire was then used to assist in the placement of the electrode lead, which traveled through the venous system into the right ventricle where the electrode was embedded. LV lead placement is generally performed subsequent to RV lead placement, with the RV lead providing a backup in case of accidental damage to the electric fibers of the heart, causing an asystolic event. As with the RV lead, a guide wire is first inserted, allowing for the insertion of a multi-delivery catheter. The catheter is subsequently maneuvered to the opening of the CS in the right atrium. From here, a contrast media is injected, allowing the surgical team to obtain a CS phleobogram to direct the placement of the lead into the most suitable coronary vein. Once the phlebogram has been obtained, the multi-delivery catheter is used to guide in the lead from the chosen vein of entry into the right atrium through the CS and into the relevant cardiac vein. LV lead placement is the most complicated and potentially hazardous element of the operation due to the significant variability of the coronary venous structure. Alterations in heart structure, fatty deposits, and valves and natural variations all cause additional complications in the process of cannulation. In the current survey, CRT was implanted in the left subclavian area in all patients. Location of the leads were investigated according to the post-operation chest radiographs. Patients with RV lead positions other than RV apex were excluded from the study, while those with LV leads in the proper position (as far as it was reachable) were included. The patients who did not have the proper anatomy for optimal lead position were excluded from the study, as well. After implantation, the corresponding electerophysiologist optimized the device by ECG in order to obtain the narrowest possible QRS. The enrolled patients were followed up every three months to analyze the capture thresholds and the percentage of biventricular pacing. Ineffective capture was resolved by changing the pacing output or interventional techniques like changing the poles in LV pacing.

3.4. Echocardiographic Response to CRT

The following echocardiographic parameters were assessed using the patients' medical records: LVEF, Left Ventricular End Systolic Volume (LVESV), and Left Ventricular End Diastolic Volume (LVEDV) measured via the Simpson's method. Echocardiographic response to CRT was defined as one of the followings: 1 - 5% increase in ejection fraction, 2 - 10% decrease in LVEDV, and 3 - 15% decrease in LVESV.

3.5. Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences, version 17 (SPSS Inc. Chicago, IL, USA). Echocardiographic parameters were presented as mean ± standard deviation and were compared before and after CRT implantation using paired t-test. In addition, categorical variables were displayed as proportions. McNemar test was used to assess the proportions of echocardiographic parameters at baseline and after CRT implantation. P-values less than 0.05 were considered to be statistically significant.

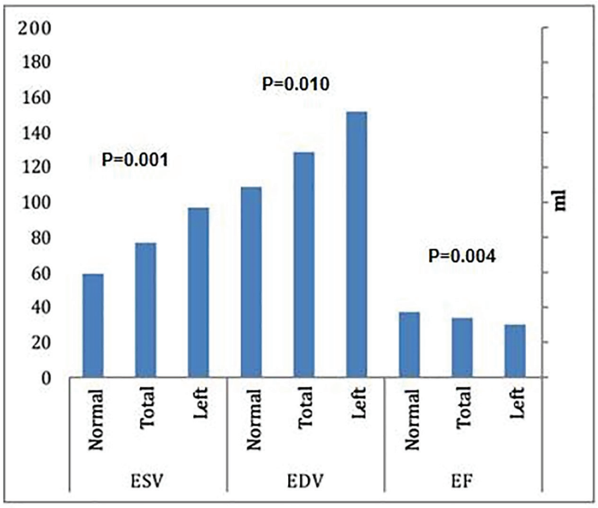
4. Results

This retrospective single-center analysis was done on

95 eligible cases with LBBB in the normal sinus rhythm during March 2012 to March 2014. These patients were divided into two groups according to the main axis of QRS. There were 48 patients with normal QRS axis and 47 ones with left axis deviation. No significant differences were observed between these two groups with respect to age, gender, frequency of ischemic cardiomyopathy and non-ischemic cardiomyopathy, NYHA functional class, baseline echocardiographic findings, and number of hospitalizations six months before CRT implantation (Table 1).

The patients were followed up for six months (post implantation) and were programmed to have adequate biventricular pacing (> 95% biventricular). The clinical and echocardiographic parameters were re-evaluated to detect any improvements in the parameters. According to the results, 71% of the patients responded to resynchronization (CRT responders). The response rate to resynchronization was 65.9% in the left axis group and 77.3% in the normal axis group, and the difference was statistically significant (P = 0.013). The results also revealed an increase in ejection fraction (P = 0.004), a decrease in LVEDV (P = 0.010), and a decrease in LVESV (P = 0.014) following CRT implantation (Figure 1). Nonetheless, these echocardiographic changes were not translated to clinical symptoms. Moreover, no significant difference was found between the two groups regarding improvement in NYHA class (P = 0.066) (Tables 2 and 3).

Figure 1. The Effect of QRS Axis on Reverse Remodeling



P-values represent differences between normal axis and left axis patients.

Table 1. Baseline Characteristics of the Patients with LBBB

Variable		LBBB with Normal Axis	LBBB with Left Axis Deviation	All Patients	P
Number		48 (50.5%)	47 (49.5%)	95	
Age		55.83	56.25	56.04	0.876
Gender	**Male**	25(52.1%)	24(51.1%)	49(51.6%)	0.921
	Female	23(47.9%)	23 (48.9 %)	46(48.4%)	
QRS duration		134.79 ± 16.85	138.09 ± 19.06	136.42 ± 15.96	0.374
Cause of HF	**ICMP**	14 (29.2%)	18 (38.3%)	32 (34%)	0.384
	NICMP	34 (70.8%)	29 (61.7%)	62 (66%)	
Hospitalization		1.34 ± 1.23	1.80 ± 1.43	1.59 ± 1.36	0.111
LVEF (%)		22.76 ± 6.82	22.84 ± 6.73	22.80 ± 6.90	0.956
LVEDV (mL)		149.45 ± 72.2	159.93 ± 59.44	153.71 ± 66.00	0.462
LVESV (mL)		91.40 ± 59.88	98.88 ± 64.17	94.40 ± 53.52	0.521
NYHA		3	3	3	0.896

Abbreviations: HF, heart failure; ICMP, ischemic cardiomyopathy; NICMP, non-ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; NYHA, New York Heart Association functional class; Hospitalization, number of hospitalizations within six months before CRT implantation

Table 2. Response to CRT after Six Months in Patients with LBBB

Variable	LBBB with Normal Axis	LBBB with Left Axis Deviation	All Patients	P
Hospitalization	0.11	0.52	0.34 ± 0.77	0.013
LVEF (%)	36.90	29.26	33.45 ± 11.02	0.004
LVEDV (mL)	108.30 ± 65.55	151.30 ± 80.56	151.30 ± 80.56	0.010
LVESV (mL)	58.80 ± 57.03	96.14 ± 74.68	76.40 ± 67.79	0.014
NYHA	2 (1 - 2)	2 (1 - 2)	2 (1 - 2)	0.066

Abbreviators: LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; NYHA, New York Heart Association functional class; Hospitalization, number of hospitalizations within six months before CRT implantation

Table 3. Changes in Echocardiographic Parameters after Six Months

Variable		LBBB with Normal Axis	LBBB with Left Axis Deviation	P-value
EF (%)	**Change**	14.63 ± 13.02	6.58 ± 8.17	0.001
EDD (mL)	**Change**	-6.07 ± 8.42	-1.58 ± 5.73	0.006
	% Change	-8.62 ± 14.25	-2.69 ± 8.85	
LVESD (mL)	**Change**	-7.60 ± 10.34	-2.71 ± 6.67	0.015
	% Change	-12.73 ± 19.32	-5.63 ± 12.30	

Abbreviations: LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; NYHA, New York Heart Association functional class; Hospitalization, number of hospitalizations within six months before CRT implantation

5. Discussion

Although controversy exists in the exact proportion of cardiac failure cases with conduction abnormalities, roughly up to 30% of heart failure patients exhibit intra-cardiac conduction abnormalities, including LBBB, and are candidate for CRT implantation (14). In spite of numerous critics about the efficacy and survival benefits of CRT, the recent large scale surveys have proved that CRT could improve cardiac function, survival, risk of arrhythmic events, and reverse cardiac remodeling (15). However, this therapeutic modality is a long and hard procedure and is expensive, especially in third-world countries. Thus, investment on finding individuals with better outcomes may help some economic sparing due to wiser distribution of the health budget.

Response to CRT is basically an aggravation of intrinsic reverse remodeling. Hence, extension of reverse remodeling can be used to predict CRT outcome (16). In the present study, LBBB with normal QRS axis was found to be associated with a better echocardiographic progress in comparison to LBBB with left axis deviation amongst CRT implanted patients. Response to CRT can be measured based on change in NYHA functional class in appropriate post operation time in addition to six-minute walking test, quality of life, and/or evaluation of echocardiographic parameters. The previous studies showed cumulative improvement in cardiac function and/or clinical status in about two-thirds of the CRT implanted patients who were considered as responders, which was in agreement with the current study results (16).

Many studies have evaluated clinical and para-clinical parameters to predict response to CRT. There is also a scoring system to predict the responders (17). Patient selection according to positive predictive factors results in having a greater percentage of responders. Although using these factors is not a part of guidelines, they can be used in situations where economic factors influence patient selection. Yet, controversies exist among studies regarding the predicting factors, which may be mainly attributed to the divergence of the issues under investigation. Nevertheless, seven factors have shown similar results. These factors include female gender, QRS duration more than 150 msec, non-ischemic cardiomyopathy, LBBB, absence of r wave in lead V1, prior heart failure hospitalization, LVEDV more than 125 mL/m2, and left atrial volume less than 40 mL/m2 (18). Furthermore, the current study results demonstrated the negative effect of left axis deviation on the clinical parameters after CRT implantation. For instance, lower hospitalization was reported among the patients with normal QRS axis ($P = 0.013$). However, the two groups were similar with regard to improvement in NYHA functional class. Since subjective issues can be traced in the evaluation of NYHA, the number of admissions seems to be more reliable although both have been mentioned in many surveys. The present study findings can be hypothesized when left axis deviation is considered as a demonstration of more peripheral involvement of the left bundle branch. Higher distal involvement may be noted as a higher depolarization front progress, which means less delay between the septum and the lateral wall. Less delay can be a reason for lower response. This theory can be supported by the similar proof for the presence of r wave in V1 as a predictor for poor response. Deep insight to the r wave in V1 clarifies it as a more distal lesion in the left bundle branch.

Up to now, no study has evaluated echocardiographic parameters for response to CRT with regard to QRS axis. The present study evaluated the impact of axis deviation on echocardiographic parameters. According to the results, patients with normal axis deviation showed better changes in echocardiographic parameters in response to cardiac resynchronization (Table 3). Echocardiographic parameters like end systolic volume, end diastolic volume, and even ejection fraction also improved significantly in the cases with normal axis LBBB compared to those with left axis deviation. These findings can be justified by the fact that patients with normal axis deviation can benefit from a less advanced disease or better conduction of electrical activity in the left ventricle, which has been considered as a more distal progress of the depolarization front. However, the first hypothesis is far from proof, because no statistically significant differences were detected between the clinical and echocardiographic variables in the present survey.

Scientists have diagnosed bundle brunch blocks in an erroneous way for nearly five decades, and a recent survey showed that a great percentage of LBBBs are actually LV hypertrophies with simultaneous right anterior hemiblocks (19). Thus, it seems reasonable to conduct further investigations about the conductive system of the heart and its diseases. The present article was a trial in this area, which showed the clinical differences between the LBBBs with positive QRS in both leads I and II in contrast to those with positive QRS in lead I but negative QRS in lead II. More proximal block to intraventricular conduction that is present in patients with normal QRS axis causes less distal penetration of the depolarization front, which seems to be the reason for higher delay in the lateral wall compared to the septum. This higher delay can imply higher dyssynchrony and can finally lead to better cardiac resynchronization after CRT implantation.

5.1. Conclusion

Clinical and echocardiographic response to cardiac resynchronization in CRT patients might decrease in the presence of QRS left axis deviation. Therefore, QRS axis can be used as a prognostic parameter to select better CRT responders.

5.2. Clinical Trial Registration Code

This was a retrospective research.

5.3. Ethical Approval

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.053).

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Authors' Contribution

The original idea and design was suggested by MHN.

Acquisition of data was performed by SB, analysis and interpretation of data in addition to drafting was provided by MA, critical revision of article for important intellectual content was a job by MVJ, study supervision and technical and material support was provided by AA and SS. The article is submitted by MHN.

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The authors have no financial interests related to the material in the manuscript.

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