



Impact of Cardiac Resynchronization Therapy on Cardiac Electric Remodeling and its Clinical and Echocardiographic Correlation

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Abstract

Aim: impact of cardiac resynchronization therapy on cardiac electric remodeling and its clinical and echocardiographic correlation.

Patients and Methods: 50 patients candidate for CRT were included and assessed before and 3 months after implantation by history taking, clinical examination, transthoracic echocardiogram, ECG and six minutes walk test.

Results: 50 patients (35 males and 15 females, mean age 54.88 ± 7.48 years) with implanted CRT. All patients were in sinus rhythm, QRS duration ≥ 120 ms and LBBB. There was clinical response to CRT as NYHA class improved $p < 0.001$ and 6 min walk test $p < 0.001$, electrocardiographic response where apart from RR interval, there were significant differences in QRSD, QT, QTc, QTd, and TPE between pre and post CRT measurements ($P < 0.001$) and echocardiographic response as LV volume improved in 78%, EF in 14% and change (Δ QRSD) significantly correlated with changes in NYHA, LVEDD, LVESD, and LVEF. (Δ QTd) significantly correlated with change in NYHA but not with echocardiographic changes. But (Δ TPE) significantly correlated with LVEDD, LVESD, LVEDV, LVESV, and LVEF but not with Δ NYHA. Area under the curve was 0.813 for Δ QRSD ($p = 0.005$), 0.56 for Δ QT ($p = 0.56$), 0.59 for Δ QTc ($p = 0.41$), 0.823 for Δ QTd ($p = 0.004$), and 0.8 for Δ TPE ($p = 0.007$). Δ QTd of ≥ -20 ms had highest sensitivity for predicting both clinical and Echocardiographic response, while Δ QRSD of ≥ -20 ms had highest specificity.

Conclusion: CRT induced reverse electric remodeling including depolarization and repolarization changes on unpaced ECG that was associated with reverse structural remodeling and clinical improvement.

Introduction

Heart Failure (HF) represents approximately 1–2% of the adult population in developed countries with the prevalence rising to $\geq 10\%$ among persons 70 years of age or older [1]. There are many causes of HF; however the most common cause of HF is coronary artery disease [2]. What characterizes untreated systolic dysfunction is progressive worsening of these changes over time, with increasing enlargement of the left ventricle and decline in EF, even though the patient may be symptomless initially. The goals of treatment in patients with established HF are to relieve symptoms and signs, prevent hospital admission and improve survival [3].

The idea of CRT is based on the concept of improving dyssynchronous conduction of the heart by biventricular pacing which leads to a significant alleviation of symptoms and increase

in exercise capacity. On average, NYHA function class decreased by 0.5–0.8 points, the 6 min walk distance increased by 20%, and peak oxygen consumption increased by 10–15%. The functional benefits and quality of life improvements were sustained [4].

A consistent finding in the randomized trials designed with up to 6 months of follow-up has been an up to 15% absolute reduction in LV end-diastolic diameter and up to 6% increase in LVEF following CRT [2]. REVERSE trial showed a significant degree of reverse LV remodeling was observed among the patients assigned to CRT, manifested by decreases in the LV end systolic and diastolic volumes and an increase in LVEF [2]. Non responders to CRT (defined as patients who doesn't show decrease in NYHA classification more than 1 within 3 months after CRT) have been defined in one third of the patients [5].

Electric remodeling in HF occurs due to left ventricular dyssynchrony and it can be predicted by the following:

QRS duration: in patients with HF, left ventricular electrical dyssynchrony is associated with QRS prolongation, it would predict the mechanical dyssynchrony therefore can predict the response to CRT based on the idea of biventricular pacing will decrease the left ventricle dyssynchrony thus will decrease QRS duration [6].

QT interval, QT dispersion & QTc

They are considered to be sensitive indicator of left ventricular dyssynchrony. We can assume that QT dispersion becomes longer when cardiac pathological changes occur causing left ventricular dyssynchrony and will be improved after CRT, thus can be a good predictor of reverse electrical remodeling following CRT [7].

T wave morphology & T peak -T end dispersion

T wave amplitude variability (TAV) can be a promising non invasive predictor of arrhythmogenic events in patients with cardiomyopathy. The decrease in TAV after CRT is associated with left ventricular reverse remodeling and it indicates reduction of the arrhythmogenic event, so it can be of good predicting value for patients follow up after CRT [7].

Aim

Impact of cardiac resynchronization therapy on electric remodeling of the heart and its clinical and echocardiographic correlation.

Patients and Methods

The study was conducted on fifty patients who are candidate for CRT at National Heart Institute in the period from October 2014 to June 2015. All patients had CRT-P devices (St. Jude) and were assessed before and at least three months after implantation

Inclusion criteria:

All patients fulfilled all the following criteria:

- New York Heart Association (NYHA) functional class III or ambulatory class IV in hemodynamically stable condition for at least 4 weeks despite optimal medical treatment.
- Left ventricular ejection fraction (LVEF) less than or equal to 35% as assessed by echocardiography.
- Intraventricular conduction delay defined by a QRS duration ≥ 120 m sec if LBBB or >140 msec if non LBBB,
- All patients were on optimal recommended pharmacological therapy including (ACE inhibitors or ARBS, B blockers, Aldosterone antagonists and diuretic).

Exclusion criteria:

- NYHA class I or II.
- Narrow QRS complex.
- Ejection fraction more than 35%.
- Presence of atrial fibrillation.
- Amiodarone therapy.
- Device malfunctions.

Each patient was subjected to history taking, clinical examination, transthoracic echocardiogram, 12 lead surface ECG and six minutes walk test before implantation and followed by reevaluation at least three months after implantation. ECGs were done with CRT off mode to acquire native electrocardiograms then Echocardiography and six minutes walk test were done for every patient to assess response.

Investigations

ECG acquisition and analysis:

Standard 12-lead surface ECGs with a paper speed of 25 mm/s and 10 mm/mV gain were analyzes prior to and at least three months after implantation while setting the device to CRT-off mode. CRT-on mode was restored after acquiring ECGs. Measurements were assessed manually and taken from the average of 2 measurements made by 2 Cardiologists who were blinded to each other's measurements and to patients' data. The following measurements were taken:

- PR interval (normally 0.12 to 0.20 sec)
- Intrinsic QRS duration (QRSD) and axis (The entire QRS duration normally lasts from 0.06 to 0.10 seconds) .
- QT interval measured from the beginning of QRS to the end of the T-wave defined as the point of return to the isoelectric line. QTc interval was calculated by Bazett's formula ($QTc = QT / \text{square root of RR interval in seconds}$). Intervals were measured in the lead with the highest T wave amplitude among leads II, V5, or V6, using the same lead in pre and post-CRT ECGs (The normal value for the QTc in men is ≤ 0.44 sec and in women is ≤ 0.45 sec)
- QT dispersion (QTd), defined as the difference between the longest and shortest QT interval among all lead (normal values from 10 to 71 ms)
- T wave peak to end (TPE) duration, defined as the duration from the peak to the end of T wave in II, V5, V6 according to the highest T wave amplitude, using the same lead in pre and post-CRT ECGs.

Echocardiography

Trans-thoracic echocardiographic examination with

machine-integrated ECG recording was performed, mostly with the patients lying in the left lateral decubitus position, using a Vivid 5 Dimension machine with an M4S matrix sector array probe with a frequency range of 1.5 to 3.6 MHz (GE Vingmed Ultrasound, Horten, Norway). Left ventricular EF, dimensions and volumes (LVEDV & LVESV) were measured utilizing modified Simpson's equation (The endocardium of the apical two and four chamber echocardiographic views in systole and diastole is traced manually).

Wall motion abnormality at rest and was assessed for patients by dividing the left ventricle into 16 segment and assessment of each segment according to the American Society of Echocardiography as follow;

- I. normal
- II. hypokinesis
- III. akinesis
- IV. dyskinesis

Mitral regurgitation

Degree of mitral regurgitation were assessed before and after CRT implantation according to The 2003 American Society of Echocardiography's consensus statement on echocardiographic quantification of valvular regurgitation and classified into (mild to moderate, moderate to severe mitral regurgitation according to jet area measurement as follow Mild < 4 cm, moderate 4-8cm and severe >8cm).

Left atrium Diameter

Was assessed for every patient pre and at least three months after CRT implantation in the PLAX view. Pulmonary artery systolic pressure: for diagnosis of Pulmonary hypertension PASP was estimated from the tricuspid regurgitant jet velocity using the modified Bernoulli equation and adding the estimated right atrial pressure (RAP) on the basis of inferior vena cava (IVC) diameter and collapsibility as follow IVC ≤ 2 cm and $>50\%$ collapsibility, 5 mm Hg; IVC >2 cm and $\geq 50\%$ collapsibility, 10 mm Hg; IVC >2 cm and $<50\%$ collapsibility, 15 mm Hg; and IVC >2 cm and no collapsibility, 20 mm Hg. We assumed RAP 10 mm Hg for cases with IVC ≤ 2 cm and $\leq 50\%$ collapsibility.

6min walk distance

Which is a simple objective measurement to assess patient's functional capacity.

Technique:

- A. Flat, straight corridor 30 m (100 feet) in length.
- B. Turnaround points marked with a cone.
- C. Patient should wear comfortable clothes and shoes.

- D. Patient rests in chair for at least 10 minutes prior to the test (ie, no warm-up period)
- E. Record baseline heart rate and blood pressure.
- F. Instruct the patient to walk as far as possible for 6 minutes.
- G. At the end of the test, the spot where the patient stopped was marked at the floor.
- H. The distance walked was recorded and calculated. (Borg GA. 1982)
- I. The test was performed to each patient before and at least three months after device implantation.

Implantation data: Pacing leads were inserted through standard subclavian vein approach. The RA lead was placed in RA appendage, The RV lead tip was placed in the apex of the right ventricle. The LV lead tip was placed in the posterolateral cardiac vein when possible or in an alternative posterior or lateral vein. The location chosen for LV lead was that giving the greatest spatial separation from the tip of the RV lead, with stable LV capture and without diaphragmatic capture at four times threshold voltage. Device programming was done during follow up of the patients in the outpatient clinic to assess lead impedances, pacing, sensing thresholds, optimization of AV and VV delays and detection of device malfunction.

Complication of CRT:

Complications of CRT implantation include coronary sinus or coronary vein trauma, pneumothorax, diaphragmatic/phrenic nerve pacing, and infection were assessed for all patient.

Criteria of CRT Response:

Response to CRT can be divided into 2 main categories: clinical end points indicating improved clinical status (NYHA functional class by ≥ 1 NYHA class, quality-of-life, exercise capacity expressed as 6-min walking distance) and Echocardiographic end points indicating improved LV systolic function or reversed LV remodeling (decrease in LV end systolic volume by $\geq 15\%$) [6].

Electrocardiographic predictor to clinical and Echocardiographic response is defined as decrease in intrinsic QRS duration by ≥ 20 ms [8].

Statistical Analysis

Continuous variables were expressed as mean \pm Standard deviation. Paired and unpaired and Student's t-test and nonparametric tests were used for comparisons between baseline and follow up.

Categorical variables were expressed as numbers or percentages were analyzed with the chi-square test. D'Agostino-Pearson test for normal distribution was done and accordingly,

non parametric test was chosen when distribution was non-normal. Comparison between continuous data before and after CRT was done using paired t-test. Comparison between continuous data in responders and non responders was done using unpaired t-test or Mann-Whitney test as appropriate. Receiver operating characteristic (ROC) analysis were carried out to examine the predictive ability of ECG parameters to the response to CRT and to determine cut-off values, sensitivity and specificity for each ΔiQRS duration .The area under curve (AUC) provided a measure of the overall discriminative ability of a model.

Correlations were made using Pearson correlation coefficient or Spearman rho as appropriate. Risk assessment for ECG parameter was expressed by unadjusted odds ratio after dichotomization according to the cut off values. P value was considered significant if < 0.05.

Results

This single center, prospective study included 50 patients (35 males and 15 females, with mean age of 54.88±7.48 years) with implanted CRT device in the period from October 2014 to June 2015. All patients were assessed twice at the time of implantation and 3 months after. All patients were in sinus rhythm, with baseline QRS duration ≥120 ms and LBBB morphology. All programmable data were accepted with ≥98% biventricular pacing.

Demographic data of the studied patients

The study included 50 patients 35 males (70%) and 15 females (30%), with mean age of 54.88±7.48. In 50% of the patients the underlying etiology was ICM and the other 50% was DCM.

II. Risk factors: 24patients (48%) were hypertensive, 22 patients (44%) had diabetes mellitus, 30 patients (60%) had

dyslipidemia and 10 patients (20%) were smokers.

Clinical response to CRT

NYHA class

20 patient (40%) improved from NYHA class (III →I), 8 patients (16%) improved from NYHA class (III →II), 8 patients (16%) improved from NYHA class (IV →I),4 patients (8%) improved from NYHA class (IV →II) and 10 patients (20%) remained in the same NYHA class 3 months after CRT (Table 1).

Results of Chi-square test showed that before CRT implantation72% of the patients were NYHA class III and 28% were NYHA class IV after CRT 58% were class I, 24% were class II, 16% were class III and 2% were class IV with p value< 0.001 (Table 1).

Six minutes walk test

- a. The mean 6MHW distance at baseline was 160.40 + 28.92 meters reaching 264.04 ± 45.29 meters 3 months after CRT implantation (P value 0.001) (Table 2).
- b. The improvement in the distance was detected in 40 cases who are clinical responders that represent about 80% of studied cases (Table 2).
- c. There was statistically significant correlation between NYHA class improvement > 1 class and six minute walk distance p=0.001 (Table 3).

Electrocardiographic response to CRT:

All ECG parameters were taken without pacing (with CRT off mode) 3m after CRT implantation. Apart from RR interval, there were highly significant differences in QRSD, QT, QTc, QTd, and TPE between pre and post CRT measurements (P<0.001) (Table 4 & Figure 1).

Table 1: NYHA class improvement 3 months after CRT.

NYHA Class Improvement 3 months after CRT	Number & Percent of Improvement
From NYHA class (III →I)	20 (40%)
From NYHA class (III →II)	8 (16%)
From NYHA class (IV →I)	8 (16%)
From NYHA class (IV →II)	4 (8%)
No improvement	10 (20%)

Table 2: Difference between pre and post CRT regarding six minute walk distance.

	Six Minute Walk Distance			Paired t-test
	Range	Mean ± SD	t	p-value
Before	100.00 – 200.00	160.40 ± 28.92	-15.144	0.001
After	160.00 – 320.00	264.04 ± 45.29		

Table 3: Correlation between NYHA class improvement and results of six minute walk test.

	Six Minute Walk Distance	P-value
NYHA Class improvement > 1 class	Form (160.40 ± 28.92) to (264.04 ± 45.29)	0.001
Pts with No improvement in NYHA CLASS	From (159.50±27.92) to (163.40 ± 32.92)	0.432

Table 4: Electrocardiographic response to CRT in all patients three months after implantation.

	Before CRT	After CRT	P-value
RR (ms)	684±99.85	634±178.59	0.23
QRSD (ms)			
Mean±SD	146.33±16.29	134.33±17.15	<0.001
Range	120-180	100-160	
QT (ms)			
Mean±SD	420.33±28.46	398.66±21.29	<0.001
Range	360-460	340-440	
QTc (ms)			
Mean±SD	505.66±45.53	475.23±31.08	<0.001
Range	400-593	415-516	
QTd (ms)			
Mean±SD	58±13.23	34.66±13.82	<0.001
Range	40-80	20-60	
TPE (ms)			
Mean±SD	124±24.3	102±22.5	<0.001
Range	80-160	80-160	

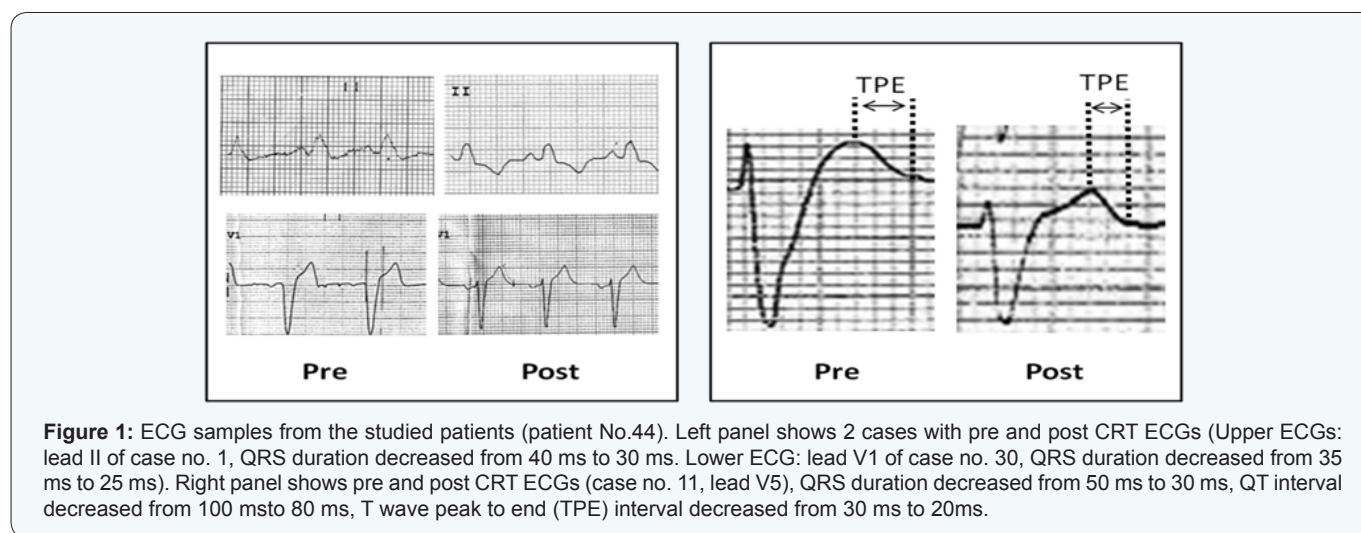


Figure 1: ECG samples from the studied patients (patient No.44). Left panel shows 2 cases with pre and post CRT ECGs (Upper ECGs: lead II of case no. 1, QRS duration decreased from 40 ms to 30 ms. Lower ECG: lead V1 of case no. 30, QRS duration decreased from 35 ms to 25 ms). Right panel shows pre and post CRT ECGs (case no. 11, lead V5), QRS duration decreased from 50 ms to 30 ms, QT interval decreased from 100 ms to 80 ms, T wave peak to end (TPE) interval decreased from 30 ms to 20ms.

Mean change in QRSD (Δ QRSD) was -12 ± 9.96 ms (median -20 ms). Δ QT was -21.33 ± 19.07 ms (median -20 ms). Δ QTc was -30.45 ± 36.03 ms (median -23.5 ms). Δ QTd was -23.33 ± 15.82 ms (median -20 ms). Δ TPE was -22 ± 22.5 ms (median -20 ms).

Echocardiographic response to CRT

- a) Regarding left ventricular volume 39 patients improved representing 78% of study cases.
- b) Regarding left ventricular ejection fraction patients with significant improvement with >10% increase in EF were 7 patients representing 14% of study cases.
- c) There was statistically significant difference in LVESV before and after CRT. P value was 0.003.
- d) There was statistically significant difference in LVEDV before and after CRT. P value was 0.002 (Table 5).

Table 5: Echocardiographic response to CRT.

	Before CRT	After CRT	P value
LVEF (%)	28.63±2.7	34.46±3.09	0.001
LVEDD (cm)	7.13±0.61	6.58±0.55	0.002
LVESD (cm)	5.16±0.91	4.68±0.8	0.006
LVEDV (ml)	268±45.66	223.83±41.96	0.002
LVESV (ml)	139.43±48.19	105.03±42.7	0.003
MR(cm ²)	5.34 ± 1.41	4.14 ± 1.01	0.01
LADiam(cm)	4.56 ± 0.41699	4.468 ± 0.37112	0.13

Correlations between changes in ECG parameters and changes in NYHA class and echocardiographic parameters

Change in native QRSD (Δ QRSD) was significantly correlated with changes in NYHA class, LVEDD, LVESD, and LVEF. (Δ QTd)

was significantly correlated with change in NYHA class but did not correlate with any of the echocardiographic changes. On the other hand, (Δ TPE) was significantly correlated with changes in LVEDD, LVESD, LVEDV, LVESV, and LVEF but did not correlate with Δ NYHA class (Table 6).

Table 6: Correlations between changes in ECG parameters and changes in NYHA class and echocardiographic parameters.

	Δ NYHA class	Δ LVEDD ^a	Δ LVESD	Δ LVEDV ^a	Δ LVESV	Δ LVEF ^a
ΔQRSD^a						
r	0.5	0.41	0.4	0.35	0.32	-0.56
P-value	0.005	0.024	0.027	0.053	0.078	0.001
ΔQT						
r	0.19	0.22	0.26	0.24	0.21	-0.35
P-value	0.30	0.23	0.15	0.18	0.26	0.051
ΔQTc						
r	0.08	0.25	0.13	0.28	0.28	-0.09
P-value	0.64	0.17	0.47	0.13	0.12	0.60
ΔQTd^a						
r	0.64	0.29	0.15	0.24	0.21	-0.23
P-value	0.001	0.11	0.41	0.20	0.25	0.21
ΔTPE						
r	0.16	0.55	0.48	0.53	0.52	-0.45
P-value	0.39	0.002	0.006	0.002	0.003	0.012

Δ : Difference between pre and post CRT values. LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; LVESV: Left ventricular end systolic volume; LVEF: Left ventricular ejection fraction; QRSD: QRS duration; QTc: Corrected QT; QTd: QT dispersion; TPE: T wave peak to end interval. Comparison was made by Mann-Whitney test due to non-normal distribution, otherwise by unpaired t-test.

ROC curve

ROC curve analysis was done to find the best cutoff values for the changes in ECG parameters associated with the clinical and Echocardiographic response to CRT (Figures 2-4). Area under the curve was 0.813 for Δ QRSD (p=0.005), 0.56 for Δ QT (p=0.56), 0.59 for Δ QTc (p=0.41), 0.823 for Δ QTd (p=0.004), and 0.8 for Δ TPE (p=0.007). Δ QTd of \geq -20 ms had the highest sensitivity for predicting both clinical and Echocardiographic response, while Δ QRSD of \geq -20 ms had the highest specificity.

Both clinical and Echocardiographic response occurred in 32 patients (64 %) who were considered as CRT responders. Clinical response without criteria of Echocardiographic response was found in 8 patients (16 %), while Echocardiographic response without clinical improvement was found in 7 patients (14 %) (Figure 5).

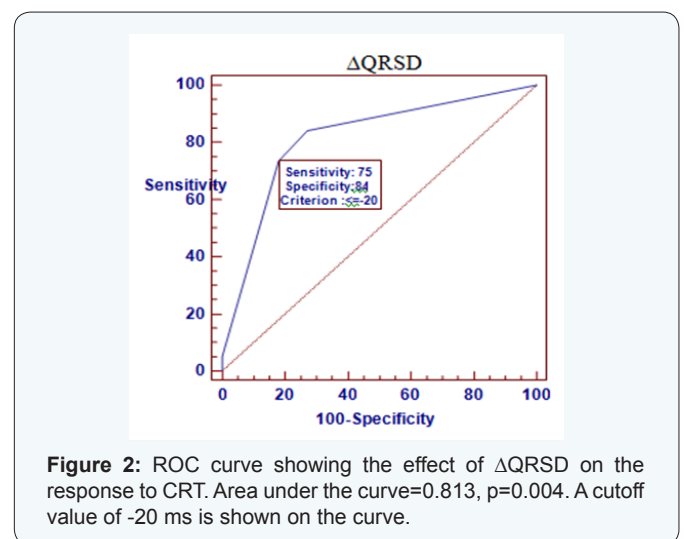


Figure 2: ROC curve showing the effect of Δ QRSD on the response to CRT. Area under the curve=0.813, p=0.004. A cutoff value of -20 ms is shown on the curve.

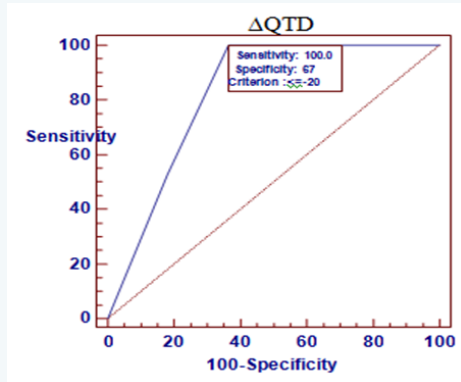


Figure 3: ROC curve showing the effect of Δ QTD on the response to CRT. Area under the curve=0.823, $p=0.005$. A cutoff value of -20 ms is shown on the curve.

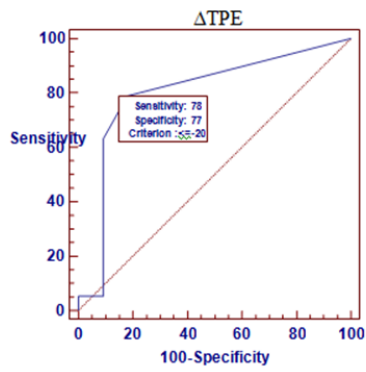


Figure 4: ROC curve showing the effect of Δ TPE on the response to CRT. Area under the curve=0.80, $p=0.007$. A cutoff value of -20 ms is shown on the curve.

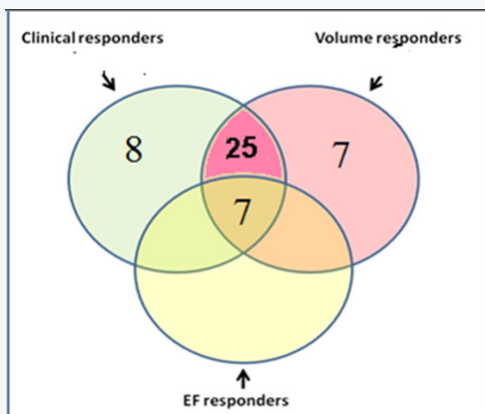


Figure 5: Clinical and Echocardiographic response.

Complications related to CRT implantation

Patients who had immediate complications after implantation of CRT represented (0.8%): 2 patients had hematomas at site of implantation representing (0.4%), 2 had diaphragmatic pacing representing (0.4%)

Discussion

Cardiac resynchronization therapy has been shown to improve heart failure, reduces hospitalization and improves the status of LV dysfunction. However, a number of patients remain unresponsive to therapy. The cause of unresponsiveness has been an issue of research in many trials and has been a concern in follow up of CRT patients [6].

Electric remodeling in HF is associated with adverse clinical outcome. Widening of the QRS complex is associated with mechanical dyssynchrony, while prolongation of repolarization is associated with ventricular arrhythmias and sudden cardiac death [3].

The main focus of this study was to evaluate the impact of Cardiac Resynchronization Therapy on electrical remodeling of the heart and its clinical and Echocardiographic correlation after three months of implantation.

In this study there were significant changes in both depolarization and repolarization parameters on surface ECG after CRT. Also there were significant differences between responders and non responders regarding changes in QRSD, QTd, and TPE. Furthermore, these changes were significantly correlated with changes in NYHA class and echocardiographic parameters. Changes in QRS duration (Δ QRSD) and repolarization heterogeneity (Δ QTD and Δ TPE) could predict response to CRT with high sensitivity and specificity [9].

Regarding CRT response

In our study, 8 patients had clinical improvement without criteria of echocardiographic response, which might be due to more patient compliance to therapy or may be placebo effect. Therefore, correlations with ECG parameters were done only in patients with both clinical and echocardiographic response who were defined as CRT responders. Response to CRT occurred in 32/50 patients (64 %), which is similar to the generally reported rate of response [10]. All CRT responders in this study had $\geq 15\%$ reduction in LVESV which is considered the hallmark of LV reverse remodeling [11]. Hence, the occurrence of ECG changes in responders indicates association between reverse electrical and structural remodeling following CRT.

Regarding RR interval

There was no significant change in RR interval on the ECG after CRT. This agrees with the studies of Henrikson and Sebag [9] who reported similar observations [9]. The pretreatment with β blocker and/or ivabradine by the majority of patients who implanted CRT may explain this finding.

Regarding QRS duration: In our study, native QRSD decreased significantly after CRT (from 146.33 ± 16.29 to 134.33 ± 17.15 ms, $p < 0.001$). This may indicate partial recovery of left bundle branch conduction. Sebag et al. [12] reported similar findings in

85 patients who were evaluated after 1 year of CRT (intrinsic QRS decreased from 168.0 ± 19.7 to 149.6 ± 31.6 ms, $p < 0.0001$). They considered patients with decrease in intrinsic QRSD by > 20 ms as “electrocardiographic responders”, who had greater rate of clinical ($p=0.035$) and echocardiographic ($p=0.023$) response [12].

Another study of Mischke et al. [13] showed that there was significant decrease in native QRSD one year after CRT device implantation [13].

Also Dizon et al. [14] reported a case with loss of LBBB and complete normalization of QRS complex after CRT [14].

In contrast to these findings of our study, Stockburger et al. [15] did not find any decrease in unpaced QRSD after CRT in a series of 21 patients. This controversy may be explained by:

- About one third of their patients were on amiodarone which influences intraventricular conduction,
- The different methods of ECG interval measurement (Stockburger et al. [15] relied on computed measurement, while our study relied on manual method)
- The variable duration in HF before CRT; longer duration might be associated with irreversible fibrotic changes [15].

Our study observed that Δ QRSD was significantly larger in responders than non responders. Δ QRSD also correlated significantly with changes in NYHA class, LV diameters, and LVEF. It was found that a Δ QRSD of ≥ -20 ms could predict response to CRT ($p=0.003$) with 75% sensitivity and 84% specificity. Similarly, [12] reported that a Δ QRSD of ≥ -20 ms was optimal for predicting both clinical and echocardiographic response. Since QRSD is well known as a predictor of total mortality and sudden cardiac death in patients with HF [16], the decrease in native QRSD after CRT may affect prognosis [16].

Tereshchenko et al. [17] reported that reduction of native QRS complex by -10 ms after CRT was associated with a fourfold decrease in the risk of death or sustained ventricular tachycardia [17].

Regarding QT and QT dispersion

In heart failure patients, the altered ion channel dynamics result in prolongation and heterogeneity of repolarization. In our study, there were significant reductions in native QT, QTc, and QT dispersion (QTd) after CRT. We did not calculate the corrected QTd (QTc dispersion) as it was previously reported that QTd is independent of heart rate [18]. Unlike Δ QT and Δ QTc, Δ QTd was significantly larger in responders than non responders, and correlated significantly with Δ NYHA class. We found that a Δ QTd of ≥ -20 ms could predict response to CRT ($p < 0.001$)

with sensitivity of 100% and specificity of 67%. In contrast to these findings; Henrikson et al. [9] and Sebag et al. [12] found no significant changes in native QT and QTc after CRT. However, since they did not exclude patients on antiarrhythmic drugs, their assessment of repolarization could not be relied upon. Despite the significant reductions in QT and QTc intervals after CRT in our study, they did not predict response to CRT [9,12].

Regarding to T wave peak to end (TPE) interval

The peak of T wave coincides with epicardial repolarization, while the end of T wave coincides with endocardial repolarization [19]. In heart failure patients, the preferential prolongation of the M cell action potential results in a transmural dispersion of repolarization (TDR), which can be estimated from the ECG as the interval between the peak to the end of the T wave [20]. TPE interval may be less dependent on cardiac depolarization changes than QT measurements, and may therefore provide a more reliable estimation of ventricular dispersion of repolarization in patients with wide QRS complex [21]. In 1081 healthy subjects, reference value of TPE interval was 94 ms in men and 92 ms in women and was independent of heart rate, therefore, does not need to be corrected [22].

In our study, baseline mean TPE interval was higher than normal (124 ± 24.3 ms), which significantly decreased after CRT. Previous studies reported that TPE prolongation was independently associated with increased risk of sudden cardiac death in cardiovascular disease [21], but not in healthy population [23]. The Reduction of TPE interval may indicate partial reversal of the adverse electric remodeling associated with heart failure. Furthermore, Δ TPE was higher in responders than non responders and correlated significantly with changes in all echocardiographic parameters that indicate reverse structural remodeling. We found that a Δ TPE of ≥ -20 ms could predict response to CRT ($p=0.001$) with sensitivity of 78% and specificity of 77%. To the best of our knowledge, there are no previous data regarding the predictive value of changes in native repolarization heterogeneity on surface ECG after CRT.

In our study 20 patient (40%) improved from NYHA class(III to I) , 8 patient(16%) improved from NYHA class (III to II),8 patient (16%) improved from NYHA class(IV to I),4 patient (8%) improved from NYHA class (IV to II) and 10 patient (20%) remained in the same NYHA classes 3 months after CRT implantation.

The results of our study are in agreement with Ypenburg et al. [24] they studied 302 patients with NYHA class III-IV and LVEF $\leq 35\%$ with a wide QRS complex, to define the rate of responders and reverse remodeling for follow up of 6 months after CRT. About 57% of the patients improved in one NYHA functional class and 12% showed an improvement of two NYHA functional classes while 31% remained unchanged at 6 months follow-up after CRT. The reason for unresponsiveness to CRT in this study

was attributed to presence of a large percentage of ischemic patients in the whole study population which accounted for 58% compared to non ischemic whom accounted for the rest of the study population [24].

The result of study of Stellbrink et al. [25] was in concordant to our study as they studied 25 patients with advanced heart failure for follow up 6 months after CRT implantation with echocardiographic measurements of both dimensions and volumes. The aim of the study was to investigate whether CRT leads to long-term improvement in LV diameters and reduces LV volumes in patients with HF and whether baseline echocardiographic variables were predictive of long-term improvement after CRT. In Stellbrink et al. [25] study the mean LVEDD and LVESD were significantly reduced after CRT. The mean LVEDD was reduced from 71 ± 10 to 68 ± 11 mm and LVESD was reduced from 63 ± 11 mm to 58 ± 11 mm respectively [25].

The author concluded that spherical shape in dilated hearts was associated with increased wall stress, and that a change in LV sphericity have been correlated to an increase in exercise capacity and may involve a reduction in regional wall stress, myocardial oxygen demand and functional MR [25].

In our study, there was statistically significant difference as regards to 6 MHW distance in clinical responders with NYHA class improvement \geq one class shows difference in the distance walked Form (160.40 ± 28.92) to (264.04 ± 45.29) three months post implantation with p value (0.001). On the other hand patients who develop no improvement in NYHA class show modest increase in distance that range from (159.50 ± 27.92) to (163.40 ± 32.92) with p value (0.432) it means that clinical responders shows corresponding increase in six minute walk test coinciding with functional class improvement. The study of Yu CM [10] was in concordant to our study .they enrolled Twenty-five patients with NYHA class III to IV heart failure and electrocardiographic wave complex duration >140 ms receiving biventricular pacing therapy were assessed serially up to 3 months after pacing, Echocardiography, six minutes walk test were performed . Echocardiography show improvement in left ventricular (LV) end-diastolic (205 ± 68 versus 168 ± 67 mL, $P < 0.01$) and end-systolic volume (162 ± 54 versus 122 ± 42 mL, $P < 0.01$); and improved 6-minute walk distance after pacing for 3 months that was considered objective measurement of clinical improvement [10].

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