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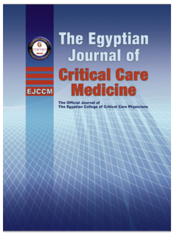

ORIGINAL ARTICLE

Temporal changes of left ventricular synchronization parameters and outcomes of cardiac resynchronization therapy

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KEYWORDS

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Abstract *Background:* Left ventricular dyssynchrony plays an important role in predicting response to cardiac resynchronization therapy (CRT).

Methods: Thirty patients underwent CRT implantation. Assessment of left ventricular (LV) dyssynchrony was done through Gated SPECT LV phase analysis.

Results: Thirty patients received CRT (mean age 58.7 ± 9.0, 24 males). CRT implantation had a favorable prognosis on cardiac functions (LVEF preimplantation: 26.8 ± 4.7% versus 29.1 ± 6.4% post-implantation; $P = 0.002$). Reverse LV remodeling ($\geqslant$15%) was documented in 19 patients. Temporal changes in LV dyssynchrony parameters were correlated to LV reverse remodeling. Applying ROC curve for LV phase analysis showed that a cutoff value of 152° for histogram bandwidth had a sensitivity of 72.7% and specificity of 63.2% for predicting CRT non-response status. Also, a cutoff value of 54° for histogram standard deviation had a sensitivity of 81.8% and specificity of 63.2%.

Conclusion: Responders of CRT showed improved LV dyssynchrony profiles. Utilizing Gated SPECT LV analysis could provide predictors for CRT non-response. Reverse LV remodeling is associated with temporal improvements in LV dyssynchrony parameters.

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1. Background

Several studies, e.g. MUSTIC, MIRACLE, COMPANION and CARE-HF studies [1–4] have demonstrated benefits of cardiac resynchronization therapy in patients with end-stage heart failure (HF), provided by multisite pacing of right and left ventricles and improving intraventricular and interventricular dyssynchrony.

Accordingly, the American College of Cardiology/American Heart Association (ACCF/AHA) guidelines have incorporated CRT implantation in managing drug-refractory HF patients with prolonged QRS duration [5]. However, applying conventional criteria, 20–40% of patients fail to respond to CRT [6–11]. It was suggested that electrical dyssynchrony represented by prolonged QRS intervals is not necessarily related to mechanical dyssynchrony, which may explain why 2040% of patients who receive CRT do not show an acceptable response [12–14]. For optimal understanding of CRT response, additional information regarding mechanical LV dyssynchrony is probably needed. Several attempts have questioned mechanical LV dyssynchrony and its impact on CRT [15–19], using different modalities e.g. tissue Doppler imaging (TDI), Gated SPECT LV phase analysis, cardiac magnetic resonance (CMR) [18,22,19,23].

Gated SPECT LV phase analysis has been introduced in 2005 to evaluate LV dyssynchronization, which would also allow for the simultaneous assessment of LV perfusion, function, and mechanical dyssynchrony [18].

In our cardiac imaging lab, we utilized this technique to examine temporal changes in LV dyssynchrony parameters across the process of CRT implantation and to explore the role of LV dyssynchrony upon CRT outcome.

2. Methods

2.1. Patient population

Thirty patients participated in this study. Patients were eligible for CRT implantation according to ACCF/AHA guidelines for managing heart failure [5]. All patients had LVEF $\leqslant$ 35%, QRS prolongation > 120 m sec, NYHA III/IV. They were maintained on guidelines directed medical therapy (GDMT) [5]. Patients with ischemic cardiomyopathy were revised for revascularization with a period of 3–6 months of follow-up. Patients who remained symptomatic i.e. NYHA III/IV, were deemed candidates for CRT implantation. All patients consented to written consent forms for participation.

2.2. Exclusion criteria

Patients with recent myocardial infarction of less than 3 months duration or dysrhythmias that could result into gating artifacts e.g. atrial fibrillation and frequents premature complexes.

2.3. Echocardiographic examination

Each patient was examined using Phillips ATL-HDI 5000 colored echocardiograph machine, with a 2.5–3 MHz transducer. Two-dimensional (2-D) and M-mode echocardiography was performed to document volumetric LV measurements. Left ventricle contractility was assessed using Simpson's method.

2.4. Rest myocardial perfusion imaging (Gated SPECT)

Patients were intravenously injected with 20–25 mCi Tc-99 m SestaMIBI. Acquisition of SPECT images was performed within 1 h of the injection of the Tc-99 m SestaMIBI using dual head Siemens gamma camera (Symbia E) utilizing Cedars-Sinai software 1994–2009, (8 frames per cycle) [20]. Analysis of Gated SPECT images was performed using Syngo MI VA60A workstation (QGS, QPS and phase analysis).

Images were gated to the R-wave of the ECG, and image acquisition was interrupted for one beat if the R–R interval varied by 15% of the preceding R–R interval. Thirty-two views with 20 s each, over 180° arc, with the patient in the supine position head in. Then, processing and filtering of the SPECT images were done using back- projection technique to get the trans-axial image, then short axis, vertical long axis, and horizontal long axis slices. Global functions quantified from gated perfusion SPECT images included left ventricular ejection fraction (LVEF), end-diastolic volume (EDV) and end-systolic volume (ESV).

The seventeen segment model was used for quantitative analysis of radioactive tracer uptake. Segments were scored visually according to tracer uptake defect percentage into five categories; ((0) No tracer uptake defect; (1) 0–25% tracer uptake defect; (2) 25–50% tracer uptake defect; (3) 50–75% tracer uptake defect; (4) 75–100% tracer uptake defect). The highest attainable score is 68. Scar burden was calculated by summing all segment scores; summed rest score (SRS) and dividing SRS by 68. All images were interpreted by a consensus of 2 nuclear cardiology readers and controversial issues were judged by a senior nuclear cardiologist.

2.5. Phase analysis of gated SPECT

Throughout the cardiac cycle, amplitude and phase of systolic wall thickening were extracted from the regional LV count changes throughout the cardiac cycle. Imaging was done with ECG-gated SPECT by use of 8 frames per cardiac cycle. The analysis used first-harmonic fast Fourier transform to approximate the wall thickening data to calculate a phase angle for each region, with 0° corresponding to the peak of the R-wave and one R–R interval corresponding to 360° [18]. Histograms of the calculated phase arrays were obtained and the following quantitative indices were calculated from each phase array: *Histogram bandwidth (H. BW)*: includes 95% of the elements of the phase distribution in degrees, *Histogram Standard Deviation (H. SD)*: is the SD of the phase distribution in degrees.

2.6. Pacemaker implantation

CRT-P/D devices were implanted in the left infraclavicular region. The left ventricular lead was inserted via the coronary sinus.

After 6 months, all patients were subjected to transthoracic echocardiography (TTE) and Gated SPECT phase analysis assessment.

Response was stated as a change of at least 15% decrease of LVES from initial baseline measurements (reverse LV remodeling), using TTE. Patients were divided into two groups, i.e. responders versus non-responders.

2.7. Statistical analysis

Numerical variables were described as mean ± SD. Categorical variables were described as percentages. Comparisons were done using Student "*t*" test for numerical variables, paired "*t*" test for paired comparisons and Chi-square test for categorical variables. Correlations were plotted and *r* values (correlation coefficients) were stated. ROC curves were plotted to determine cutoff values. *P* was considered significant if $\leqslant 0.05$. Statistics were calculated using IBM® SPSS® Statistics version 20 [21].

3. Results

The mean age of studied patients was 58.7 ± 9.0 years old (range 37–71). Twenty-four males were included in our study (80.0%). Echocardiographic response was illustrated in 19 patients (63.3%). Table 1 shows baseline characteristics for recruited patients. In our 30 patients, defects in radioactive tracer uptake comprised 31.8% of examined segments. Summed rest score was 13.9 ± 5.1, with a scar burden of 23.8 ± 8.5%.

Comparison between responders and non-responders showed no significant difference between both groups for their baseline LV volumes and contractility. Tables 2 and 3) and Fig. 1 shows pre-CRT and post-CRT volumetric echocardiographic data.

Left ventricular dyssynchrony assessment through LV phase analysis showed significant differences between responders and non-responders; where non-responders showed higher degrees of histogram bandwidth and histogram SD as in Table 4. Left ventricular phase analysis parameters were also correlated to resting perfusion defect i.e. SRS (histogram BW: *r* .517, *P* .003 and histogram SD: *r* .480, *P* .007).

Non-responders showed higher scar burden i.e. summed rest score for non-responders was 17.5 ± 4.0 versus 15.6 ± 6.9 for responders and scar burden was 25.4 ± 5.9% for non-responders versus 22.9 ± 9.8% for responders, but this did not reach statistical significance. Rest perfusion defect comparison between responders and non-responders is shown in Table 5.

Temporal changes across LV phase parameters are shown in Table 6 and Fig. 2. All patients showed significant improvement in their dyssynchrony profile but responders and non-responders did not show the same magnitude of improvement as shown in Table 7. Patients with lower magnitudes of reverse LV remodeling tended to show higher degrees of dyssynchrony as shown in Table 8 and Fig. 3. Through further analysis, LV reverse remodeling was correlated to phase analysis parameters; (Histogram bandwidth: *r* .387 – *P* .034, and for histogram SD: *r* .379 – *P* .039) and to changes in LV phase analysis parameters; (Histogram bandwidth: *r* .785 – *P* < .001 and histogram SD: *r* .793 – *P* < .001).

Table 1 Comparison of demographic data between responders and non-responders.

All patients	Responders	Non-responders	*P*
Age	55.3 ± 10.6	57.7 ± 9.8	NS*
Gender (female)	5 (26.3%)	1 (9.1%)	NS
Diabetes	5 (26.3%)	6 (54.5%)	NS
Smoking	11(57.9%)	7 (63.6%)	NS
Hypertension	8 (42.1%)	9 (81.8%)	NS
ICM	12 (63.2%)	9 (81.8%)	NS
Pre-CRT QRS duration	144.2 ± 12.6	147.3 ± 11.9	NS

* NS: Non-significant.

Table 2 Comparison between responders and non-responders, prior to and post CRT implantation (TTE).

Echocardiography		Responders	Non-responders	*P*
Pre-implantation	LVES	145.4 ± 18.2	148.6 ± 21.1	NS
	LVED	200.8 ± 30.5	201.6 ± 28.8	NS
	LVEF%	27.2 ± 4.9	26.2 ± 4.6	NS
Post-implantation	LVES	116.9 ± 16.4	147.3 ± 22.1	**< .001**
	LVED	155.2 ± 250	184.0 ± 26.8	**.006**
	LVEF%	32.5 ± 6.1	25.1 ± 5.1	**.002**

A multiple regression was run to predict LV remodeling, (from histogram bandwidth, histogram SD, delta change in histogram BW, and delta change in histogram SD). All variables were insignificant predictors, apart from delta change of histogram SD (Beta = .780, *P* .010) with R^2 = .767.

ROC curve was also plotted in Fig. 4 to determine possible cutoff for LV histogram bandwidth and SD that could predict potential CRT non-responders, BW:(Cutoff: 152, AUC 72.2%, sensitivity 72.7%, specificity 63.2%, *P* .045), SD: (Cutoff: 54°, AUC 74.2%, sensitivity 81.8%, specificity 63.2%, *P* .03). Neither LV volumes nor contractility could predict CRT outcome. Patients were divided according to our proposed histogram SD into those $< 54°$ and $\geqslant 54°$. Comparison between both groups was tabulated into Table 9.

4. Discussion

This was a prospective non-controlled study recruiting 30 patients who were eligible for CRT implantation according to ACCF/AHA guidelines for managing heart failure [5]. Cardiac resynchronization therapy was performed in Critical Care department (Cairo University). Patients were followed-up for a period of six months duration.

Cardiac resynchronization therapy responders had better LV reverse remodeling response with improvement in contractile properties in our study. This has been in agreement with other studies where potential effects of cardiac resynchronization therapy had been demonstrated upon LV reverse modeling and functional improvement [1–4]. Cardiac resynchronization therapy is an established therapy for patients with advanced heart failure who have prolonged QRS duration and has been incorporated into recent end-stage HF guidelines [5].

Several attempts were done to quantify mechanical LV dyssynchrony and revealed that LV mechanical dyssynchrony is an important predictor of response to CRT. Several techniques were explored e.g. tissue Doppler imaging (TDI), Gated SPECT LV phase analysis, cardiac magnetic resonance – tissue synchronization index (CMR-TSI), circumferential uniformity

Table 3 Comparison between prior to and post CRT implantation by TTE in both responders and non-responders.

Echocardiography		Pre-CRT	Post-CRT	*P*
Non-responders	LVESv (ml)	148.6 ± 21.1	147.3 ± 22.1	NS
	LVEDv (ml)	201.6 ± 28.8	184.0 ± 26.8	**.002**
	LVEF%	26.2 ± 4.6	25.1 ± 5.1	**.025**
Responders	LVESv (ml)	145.4 ± 18.2	116.9 ± 16.4	**< .001**
	LVEDv (ml)	200.8 ± 30.5	155.2 ± 250	**< .001**
	LVEF%	27.2 ± 4.9	32.5 ± 6.1	**< .001**

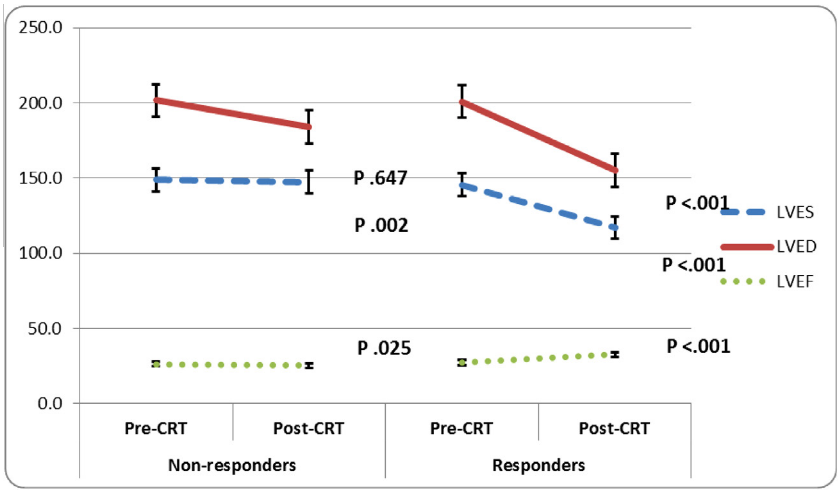

Figure 1 Temporal changes in LV volumes and contractility in both responders and non-responders, (pre- and post-CRT implantation by TTE). The solid line represents LVED, the dashed line represents LVES and the dotted line represents LVEF.

Table 4 Comparison between pre- and post-implantation cardiac imaging.

Gated SPECT		Responders	Non-responders	*P*
Pre-implantation	Histogram BW	150.7 ± 24.8	174.1 ± 32.2	**.034**
	Histogram SD	53.8 ± 9.1	61.9 ± 10.0	**.033**
Post-implantation	Histogram BW	102.8 ± 18.1	132.6 ± 22.7	**< .001**
	Histogram SD	37.6 ± 6.0	50.6 ± 9.1	**.001**

ratio estimate (CURE) [18,22,19,23]. In a prospective, multicenter setting, the predictors of response to CRT (PROSPECT) study could not provide any echocardiographic parameters to predict CRT response [24]. Cardiac magnetic resonance (CMR) is an expensive modality, requiring expertise and certain precautions. Phase analysis was first introduced with planar gated blood pool ventriculography for evaluating the contraction pattern of the left ventricle. Phase analysis using GSPECT provides comprehensive assessment of multiple parameters (e.g., LV mechanical dyssynchrony, myocardial scar burden and location), with high intraobserver and interobserver agreement [25].

Table 5 Rest perfusion defect comparison between responders and non-responders.

Gated SPECT	Responder	Non-responder	*P*
SRS	13.3 ± 5.9	14.9 ± 3.4	NS
No. segments with tracer uptake defect	5.1 ± 2.0	6.0 ± 1.3	NS
Scar burden	19.5 ± 9.7%	21.8 ± 4.9%	NS

In our study, there were no significant differences between responders and non-responders, regarding their initial baseline clinical characteristics or echocardiographic measurements. However, LV phase parameters showed significant differences between responders and non-responders, (Bandwidth: 150.7 ± 24.8 vs. 174.1 ± 32.2, *P* .037, SD: 53.8 ± 9.1 vs. 61.9 ± 10.0, *P* .033). These parameters improved significantly post-CRT implantation for both responders and non-responders.

Inability to discriminate potential responders, based upon baseline clinical or echocardiographic measurements has been emphasized by Reuter et al., who studied 102 patients and compared characteristics between responders and non-responders receiving biventricular pacing for resistant heart failure management and concluded no single clinical baseline

Table 6 Comparison between pre- and post-implantation cardiac imaging.

Gated SPECT		Pre-CRT	Post-CRT	*P*
All patients	Histogram BW	159.3 ± 29.5	113.7 ± 24.4	**<.001**
	Histogram SD	56.8 ± 10.1	42.4 ± 9.6	**<.001**
Non-responders	Histogram BW	174.1 ± 32.2	132.6 ± 22.7	**<.001**
	Histogram SD	61.9 ± 10.0	50.6 ± 9.1	**<.001**
Responders	Histogram BW	150.7 ± 24.8	102.8 ± 18.1	**<.001**
	Histogram SD	53.8 ± 9.1	37.6 ± 6.0	**<.001**

Table 7 LV reverse remodeling and delta changes in LV phase analysis parameters.

Gated SPECT	Responder	Non-responder	*P*
LVES change	−19.7 ± 3.5	−0.8 ± 6.3	**<.001**
Histogram BW delta change	−31.7 ± 4.8	−23.6 ± 3.9	**<.001**
Histogram SD delta change	−29.8 ± 6.1	−18.2 ± 6.3	**<.001**

Table 8 Relation between LV phase analysis and LV reverse remodeling.

LVES change (LV reverse remodeling)	Correlation coefficient	*P*
Histogram BW	−.387	**.034**
Histogram SD	−.379	**.039**
Delta change in histogram BW	.785	**<.001**
Delta change in histogram SD	.793	**<.001**

characteristics or echocardiographic or Gated SPECT data for LV volumes and contractility could discriminate between responders and non-responders [26].

However, association between LV dyssynchrony and CRT outcome was echoed in several studies, e.g. Bax et al. who documented significant differences in LV dyssynchrony, evaluated by TDI, between CRT responders and non-responders [27]. Also Henneman et al. studied 42 patients with severe HF and observed significant differences in responders compared to non-responders, regarding histogram bandwidth (175 ± 63° vs. 117 ± 51° [$P < 0.01$]) and phase SD (56.3 ± 19.9° vs. 37.1 ± 14.4° [$P < 0.01$]) [28]. This was also observed by Boogers et al. comparing responders versus non-responders for histogram bandwidth (94 ± 23° vs. 68 ± 21°, $P < 0.01$) and phase SD (26 ± 6° vs. 18 ± 5°, $P < 0.01$) [29]. This was also obvious in our experiment, (Histogram bandwidth: 150.7 ± 24.8 for responders versus 174.1 ± 32.2 for non-responders, P 0.034) (Histogram SD: 53.8 ± 9.1 for responders versus 61.9 ± 10.0 for non-responders, *P* 0.033).

In our study, there was a significant correlation between resting perfusion defect detected by Gated SPECT imaging and dyssynchronous LV parameters. Association between resting perfusion defect and LV dyssynchrony was explored in previous studies; Murrow et al. studied 28 subjects who underwent successful primary percutaneous coronary intervention for STEMI. In his work, baseline histogram bandwidth correlated with resting perfusion defect size ($r = 0.67$, $P < .001$), ESV ($r = 0.72$, $P < .001$), EDV ($r = 0.63$, $P = .001$), and inversely with LVEF ($r = -0.74$, $P < .001$), with improvement in histogram bandwidth over 6 months follow-up that correlated with a reduction in LV end-systolic volumes ($r = 0.43$, $P = .034$) [30]. This also goes in line with work by Samad et al. who noted that the severity and extent of myocardial scar on SPECT imaging were independent predictors of mechanical dyssynchrony [31]. This was also confirmed by Ludwig et al. who studied the effect of LV scar upon LV dyssynchrony and proposed that histogram SD values may be increased by the presence of scar [32].

Our patients who were classified 'non-responders', had higher global scar distribution and density, but this did not reach statistical significance. This could be attributed to our small sample size with possibility of type II error. However, these findings could partly explain why patients with higher LV dyssynchrony parameters, showed lower degree of reverse LV remodeling. Those patients had higher SRS scores and larger distribution of scarred segments. This was not taken into consideration in Bax, Boogers and Henneman studies. Besides, non-responders showed a lower degree of LV reverse remodeling than responders did, but this did not reach our response criterion.

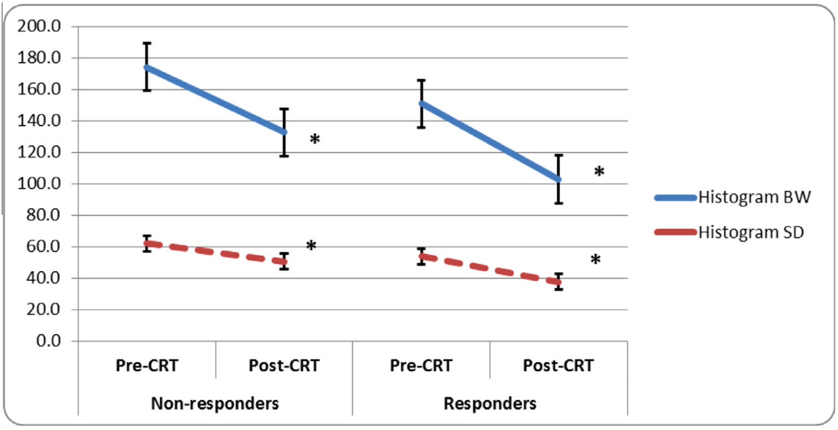

Figure 2 Temporal changes in LV phase analysis parameters for LV dyssynchrony in both responders and non-responders, (pre- and post-CRT implantation). The solid line represents histogram bandwidth and the dotted line represents histogram standard deviation. ($^{*}P$ value was <.001 for all).

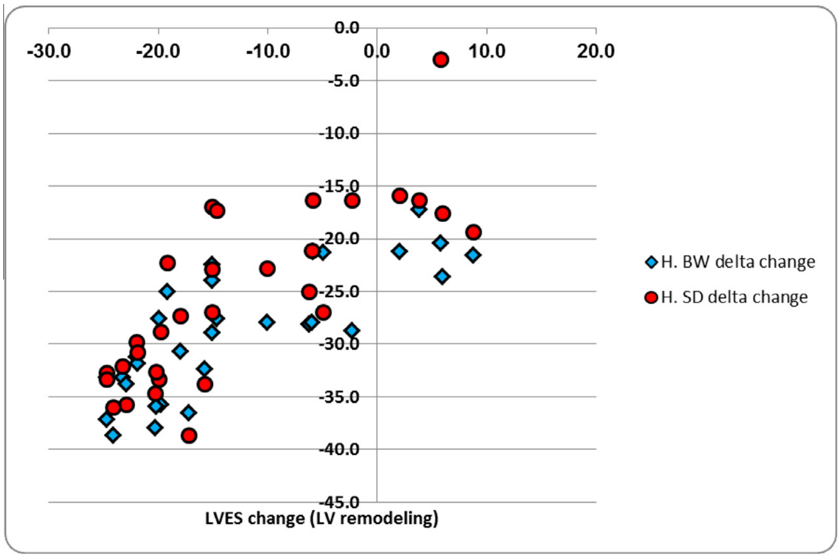

Figure 3 Correlation between LVES delta change (plotted on horizontal axis) and both histogram BW (blue rhomboid) and histogram SD (red circles), plotted on vertical axis.

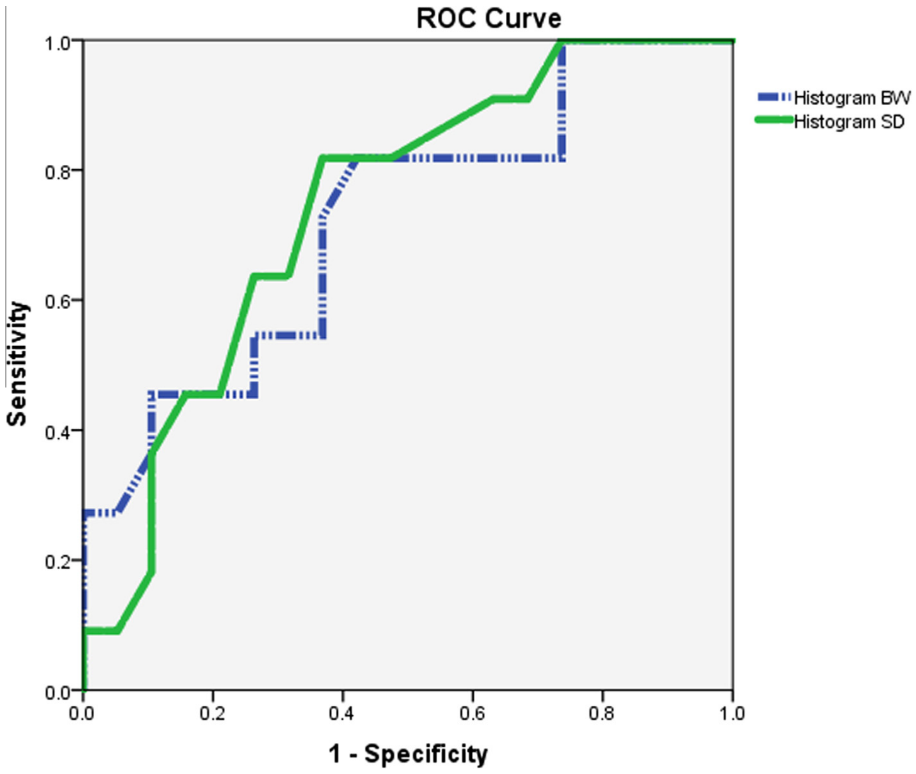

Figure 4 ROC for LV phase analysis to predict CRT non-responder. The solid line represents histogram bandwidth and the dotted line represents histogram standard deviation.

Our research showed that LV reverse remodeling correlated to phase analysis parameters and temporal changes in LV end-systolic volume correlated to temporal changes in LV dyssynchrony. This is in agreement with Brandão et al. who studied 30 patients with severe HF before and 3 months after CRT. Patients, who exhibited improvement in LVEF, showed favorable changes in EDV, ESV, LV dyssynchrony indices, and regional motion [33]. Samad et al. noted that among significant univariate predictors of mechanical dyssynchrony, enlarging left ventricular volume was associated with increasing Phase SD [31].

After applying ROC curve for LV phase analysis data to predict potential CRT non-responders, a cutoff value of 152° for histogram bandwidth had a sensitivity of 72.7% and

Table 9 Comparison between patients with histogram SD < 54° and ⩾54°.

Histogram SD criterion	H. SD ⩾ 54°	H. SD < 54°	*P*
Initial LVES	159.0 ± 16.6	137.1 ± 15.1	**.001**
Initial LVED	217.4 ± 23.7	188.7 ± 27.7	**.006**
Histogram BW	183.7 ± 25.9	140.6 ± 14.8	**<.001**
Histogram SD	65.7 ± 8.4	50.0 ± 4.4	**<.001**
LVES delta change	−8.1 ± 11.6%	−15.9 ± 8.3%	**.041**

specificity of 63.2, and also a cutoff value of 54° for histogram SD yielded a sensitivity of 81.8% and specificity of 63.2%.

Previous attempts to utilize LV phase analysis to predict CRT outcome by Boogers et al., identified a cutoff value of 72.5° for histogram bandwidth to predict CRT response. This yielded a sensitivity of 83% and a specificity of 81%. For phase SD, sensitivity and specificity similar to those for histogram bandwidth were obtained at a cutoff 19.6° [29]. Boogers cutoff values for phase analysis were different to those obtained in a study by Henneman et al. who demonstrated an optimal cutoff value of 135° for histogram bandwidth (sensitivity and specificity of 70%) and of 43° for phase SD (sensitivity and specificity of 74%) for the prediction of response to CRT [28]. Boogers attributed differences to different software packages or to differences in study populations.

5. New knowledge gained

Our observations suggested that marked LV dyssynchronous contraction could result in unfavorable response to CRT. However, LV dyssynchrony parameters could serve as an acceptable predictor for CRT non-response status.

6. Conclusion

Dyssynchronous LV contraction had a significant impact on CRT outcome. The presence of mechanical dyssynchrony could predict CRT outcome and help to discriminate non-responders.

Conflict of interest disclosure statement

No conflicts of interest to be disclosed.

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