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Research Brief

Correlation of newer indices of dyssynchrony with clinical response in patients undergoing cardiac resynchronisation therapy

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ABSTRACT

The benefits of CRT in select subsets of systolic heart failure patients with LBBB are proven. We prospectively evaluated conventional and newer echocardiographic parameters of left ventricular dyssynchrony in 35 patients who underwent CRT and were followed up after 6 months. Of the 33 surviving patients, 21 were echocardiographic responders and 24 were clinical responders. The parameters in clinical responders and non-responders were compared. The anatomic M Mode parameters of delays improved, while the radial strain and the mitral valve velocity time integral (MVVTI) did not show any significant change after CRT.

1. Introduction

Cardiac resynchronization therapy (CRT) has revolutionized management of select subsets of systolic heart failure. However, about 30% of patients who receive indicated therapy remain “non-responders” to CRT. There has been some evidence to suggest that there is a weak correlation between electrical and mechanical dyssynchrony inpredicting subsequent benefit of CRT.[2] One third of patients with prolonged QRS do not exhibit intra-left ventricular (LV) dyssynchrony,[1–3] which may explain reasons for non-response. This study evaluates baseline echocardiographic parameters of dyssynchrony in patients undergoing CRT implantation and their evolution after CRT on follow up.

2. Method

This was a prospective study comprising 35 patients aged >18 years admitted in a tertiary care hospitalfor CRT implantation based on the following conventional indication[2]: NYHA $\geq$ II, LBBB or LBBB-like pattern on ECG with QRS duration >120 ms and left ventricular ejection fraction (LVEF) < 0.35. The patients included in the study also needed to fulfil at least one echocardiographic dyssynchrony parameter as detailed below. Patients with advanced renal failure, severe mitral regurgitation, associated irreversible severe right ventricular dysfunction and expected life span less than 1 year due to comorbidities were excluded. The 6 min walk distance[4] (6MWD) was measured before CRT and on follow up. Detailed echocardiography including anatomic M-mode, speckle tracking and radial strain was performed according to a pre-decided protocol (Table 2) before and after CRT as well as on follow up, by the same echocardiographer, using the Philips Epic 7 machine. Response to CRT[5,6,7,8] was classified as echocardiographic or clinical as follows:

Echocardiographic responders (at least 2 of the following):

1. $\geq$15% reduction in LV end-systolic volume (LVESV)
2. Improvement in left ventricular ejection fraction (LVEF) $\geq$0.1
3. No evidence of dyssynchrony in conventional M-mode and anatomic M-mode after CRT
4. Increase in Diastolic filling time (DFT/RR) and Mitral valve Velocity integral time (MVVTI/RR) > 50%
5. Improvement in dyssynchrony on radial strain

2.1. Clinical responders

1 Improvement by $\geq$ 1 NYHA functional class
2 Improvement by $\geq$ 10% in 6MWD

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Table 1
Baseline demographics and medications.

AGE WISE DISTRIBUTION	
Age	No of patients
30–40	5
41–50	5
51–60	10
61–70	7
71–80	6
>80	2
SEX WISE DISTRIBUTION	
Male	Female
20	15
57%	43%
DRUGS DISTRIBUTION	
Drugs	No (%)
Digoxin	(40)
Beta Blocker	(84)
ACE Inhibitor/ARB	(88)
Diuretics	(96)
Aldosterone Antagonist	(80)
Ivabradine	(56)

Data was collected and analysed with SPSS software. A p value of <0.05 was considered significant.

3. Results

The study group included 15females and 20 males, aged 61 ± 21years. Amongst these, 17 (48%) patients were in NYHA Class IIIand 4 (12%) patients were in ambulatory Class IV despite optimum medical therapy; the remaining 14 (40%) patients were in NYHA class II. Amongst the 35 study patients, 33 could be followed up after 6 months; 2 patients expired (Table 1). All patients responded electrocardiographically post CRT (significant reduction in QRS duration compared to pre CRT) Amongst the 33 who could be followed up at 6 months, 21were echocardiographic responders and 24 were clinical responders. Of the 21 echocardiographic responders, 15 were clinical responders as well. The ECG, 6MWD and echocardiographic parameters are summarized along with respective p values in Table 3. The baseline QRS duration was 162.5 ± 18.9 ms and the LVEF was 0.22 ± 0.07. The QRS duration shortenedto137 ± 19ms ($p < 0.0001$) immediately after CRT and remained soon follow-up (138.5 ± 21, $p = 0.001$). At 6 months follow up, the LVEF increased to 0.32 ± 0.08 ($p = 0.0055$). The 6MWD increased from 256 ± 24 m to 298 ± 32 m ($p < 0.0001$) at 6 months. The left ventricular dimensions as well as conventional and anatomic M-mode delays between septal to posterior and septal to lateral walls reduced after CRT and remained so on follow-up (Fig. 1, Table 3).

Table 2
Dyssynchrony parameters.

Sr. No.	Parameters	Criteria for dyssynchrony	Criteria for response	Methodology
1	LVEF -Visual - Simpsons Method		Increase in LVEF by ≥ 10%	Apical 4 chamber view
2	LVIDd and LVIDs			PLAX view on M-mode, at level of tips of mitral leaflets
3	EDV and ESV		Decrease in LVEDV by 15% Decreased in LVESV by 15%	Assessed in 4 apical chamber view by Simpson's technique
4	Conventional M-mode Septal-Post Delay	≥130 ms	Delay <100 ms	PLAX view- mid and basal level
5	Conventional M-mode: Ant-Post delay	≥130 ms	Delay <100 ms	SAX at mid-ventricular level
6	Anatomic MMode (AMM): Septal to Lateral wall delay (SLWD); Septal to Posterior wall delay (SPWD)[109]	≥130 ms	Delay < 100 ms	SAX view at mid-ventricular level Septum @ 10 o'clock Lateral @ 4 o'clock Posterior @ 6 o'clock
7	Diastolic Flow Time (DFT)/RR	<40%	>50%	Apical 4 chamber with PW Doppler and ECG
8	MV VTI/RR		Increase by ≥ 10%	Apical 4 chamber with the help of PW on mitral valve inflow; MV VTI area traced manually
9	Radial Strain	≥130 ms	<100 ms	Measured with the help of Q lab software

Table 3
Echocardiographic Parameters pre-CRT, post-CRT and follow up.

Parameter	Pre-CRT (n = 35)	Post- CRT(n = 35)	Follow up (n = 33)	p-value (T-test)[a]
QRS	162.5 ± 18.9	137.1 ± 19.1	138.5 ± 20.8	0.0001
6 min walk test	256 ± 24	298 ± 32		<0.0001
LVIDD	62.7 ± 12.3	58.3 ± 12.0	58.2 ± 13.1	0.1379
LVIDS	49.8 ± 13.5	46.8 ± 12.9	45.3 ± 13.6	0.16481
EDV	163.0 ± 70.8	158.2 ± 77.8	147.2 ± 75.5	0.44923
ESV	122.0 ± 62.5	112.4 ± 61.5	102.1 ± 58.1	0.25497
Visual EF	22.3 ± 6.6	26.9 ± 8.2	30.9 ± 9.6	0.0001
PLAX – Basal	195.7 ± 60.3	90.9 ± 68.4	69.5 ± 58.4	0.0001
PLAX – Mid	191.3 ± 55.0	84.6 ± 57.9	71.7 ± 48.2	0.0001
DFT	387.4 ± 124.5	379.3 ± 137.8	431.8 ± 114.3	0.26162
DFT/RR	0.41 ± 0.07	0.44 ± 0.08	1.80 ± 7.46	0.25462
Mitral VTI	16.2 ± 3.6	16.4 ± 4.8	18.1 ± 5.6	0.10583
VTI/RR	0.0195 ± 0.006	0.0193 ± 0.0043	0.0213 ± 0.0061	0.30914
SAX-MID-A to P	192.0 ± 67.2	63.2 ± 75.5	51.1 ± 69.1	0.0001
SAX-MID-S to L	195.1 ± 60.0	76.4 ± 81.7	52.6 ± 56.4	0.0001
SAX-MID-S to P	221.2 ± 73.0	95.0 ± 85.3	59.3 ± 53.5	0.0001
Radial Strain - S to L - Mid	−19.4 ± 202.7	87.4 ± 218.6	88.6 ± 220.7	0.28519
Radial Strain - S to L – Basal	−67.1 ± 246.7	14.1 ± 240.6	81.9 ± 192.6	0.04011
Radial Strain - S to P – Mid	−12.7 ± 217.1	20.1 ± 199.0	67.2 ± 218.2	0.25368
Radial Strain - S to P – Basal	−88.8 ± 179.5	−32.3 ± 219.5	26.3 ± 140.2	0.03384

[a] Pre-CRT vs follow-up.

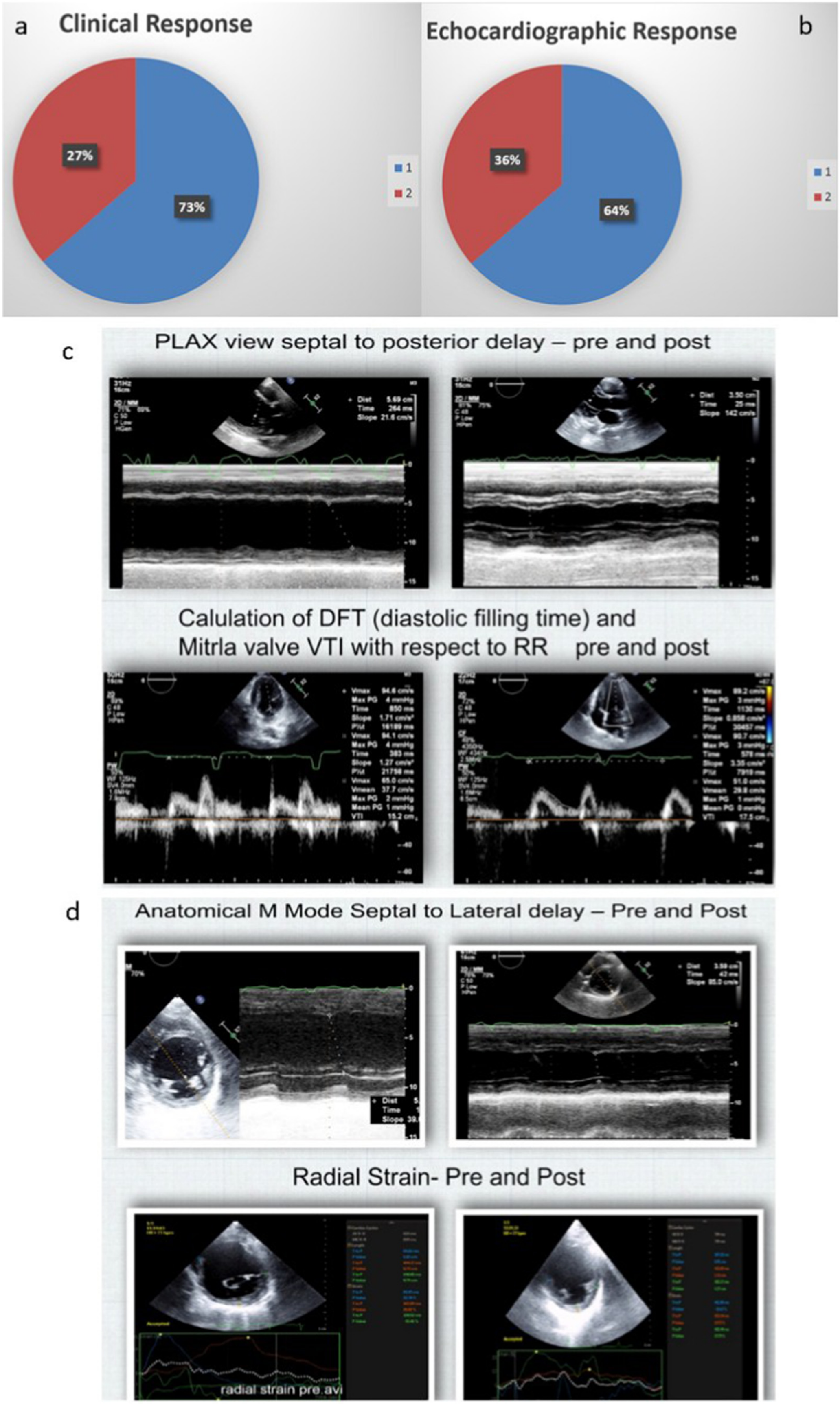

Fig. 1. a, b: shows Clinical and Echocardiographic responders (blue) and non-responders (red), c: PLAX Septal to posterior delay – Pre and Post CRT, DFT and MVVTI – Pre and post CRT, d: Anatomical M mode Septal to lateral delay – Pre and post CRT; Radial strain – Pre and post CRT.

The analysis of various Echocardiographic parameters before, after implant and on 6 months follow which ***showed*** significant change in mean values are as follows:

a) The LVIDd and LVIDs values were significantly reduced
b) The LVESV values were significantly reduced
c) The LVEF (Simpsons) values significantly improved
d) PLAX-Basal time delay between interventricular septum and posterior wall were significantly reduced
e) PLAX-Mid time delay between interventricular septum and posterior wall were significantly reduced
f) The MVDFT/RR values were significantly higher after CRT but not on follow-up, compared to the value before CRT.
g) The SAX-Mid S–P values were significantly reduced
h) The RS Mid S-L values were significantly higher after CRT, but the follow-up evaluation values did not reach significance as compared to the value before CRT.

The analysis of various Echocardiographic parameters before, after implant and on 6 months follow which ***did not show*** significant change in mean values are as follows:

a) The LVEDV values
b) The mean mitral DFT values
c) The mean mitral VTI values
d) The MVTI/RR values
e) The SAX-Mid A-P values
f) The SAX-Mid S-L
g) The RS Basal S-L values
h) The RS Mid S–P values
i) The RS Basal S–P values

4. Discussion

Recent studies examining the response to CRTindicate that none of the traditional selection criteria (NYHA class III–IV, LV ejection fraction $\leq$0.35 and QRS duration $\geq$ 120 ms) were able to reliably predict a positive response to CRT.[5–8] In search for better selection criteria, it was suggested that the key predictor of benefit from CRT could be the presence and subsequent reduction of LV dyssynchrony.[5–8] We analysed ECG and echocardiographic parameters before, after and at 6 months follow-up, to study their evolution in patients responding clinically to CRT. The patient age, comorbidities like hypertension and diabetes, baseline medical therapy, QRS duration and its decrease after CRT were quite similar as in previous major randomised trials; the gender distribution differed slightly.[9,10] Baseline LV dimensions and geometry in the study subjects was comparable to published results and so were the improvements in LVEF.

Increase in the Diastolic filling time (DFT) is expected to improve stroke volume and cardiac output leading to symptomatic benefit to the patients.[11] The trans-mitral DFT in our study did not increase significantly on follow up. Verbrugge et al[12] in 2013, in a group of 91 patients, showed that DFT/RR increase after CRT reflects favourable reverse remodelling and is associated with better clinical outcome after 6 months of CRT. In our study, we evaluated pre-CRT MVVTI/RR and on follow up, but there was no significant difference. There are relatively few studies which report on MVVTI to judge CRT response. Thomas et al[13] in 2009 in a study of 30 patients for the optimization of AV delay showed that the mitral VTI had excellent feasibility and reproducibility. Likewise there are scant data reported on use of anatomic M-mode (AMM) to judge suitability for CRT and response to CRT. In the short axis view, the AMM allows for assessing septal-posterior (SPD) and septal-lateral (SPD) delays, unlike conventional M-mode which only measures antero-posterior delay (which is anyway not the target for CRT). We found both conventional M mode and anatomical M mode showed marked reduction in mechanical dyssynchrony after CRT. Using AMM, we found SLD was reduced on follow up in those who clinically respond to CRT. Sakamaki et al[14] showed that AMM was a useful option to visualize an early septal displacement which could not be identified on the standard M-mode images and the modified method of SPD measurements could improve the ability to predict CRT response. Although our study did show that at 6 month follow up after CRT, the QRS duration and LV dimension decreased while the LVEF increased, there was no improvement in diastolic parameters such as DFT/RR and Mitral VTI/RR. The insignificant change seen in radial strain with CRT in this study may suggest its limited utility in assessing dyssynchrony and predicting a response, however it does need a longer follow up for a clearer picture.

The present study, though partly limited by sample size and duration of follow up, is a step further towards better selection for CRT and better prediction of clinical and echocardiographic response to CRT.

5. Conclusion

Novel parameters like MVVTI/RR and radial strain failed to demonstrate statistical significance in the current study. Anatomical M mode looks promising in the prediction of response to the CRT in addition to clinical and ECG criteria and could be of use for patient selection too.

References

1. Naik A, Singh B, Yadav R, et al. Cardiac resynchronization therapy is associated with improvement in clinical outcomes in Indian heart failure patients: results of a large, long-term observational study. *Indian Heart J*. 2018;70:S377–S383.
2. Yancy CW, Jessup M, Bozkurt B, et al. ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *J Am Coll Cardiol*. 2013;62(16). e147–239.
3. Swedberg K, Kjekshus J, CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *Am J Cardiol*. 1988;62(2):60A.
4. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362(9386):772–776.
5. Boidol J, Średniawa B, Kowalski O, et al. Triple-SiteVersus Standard Cardiac Resynchronisation Trial (TRUST CRT) Investigators. Many response criteria are poor predictors of outcomes after cardiac resynchronization therapy:validation using data from the randomized trial. *Europace*. 2013;15(6):835–844.
6. Bleeker GB, Bax JJ, Fung JWH, et al. Clinical bversus echocardiographic parameters to assess response to cardiac resynchronization therapy. *Am J Cardiol*. 2006;97:260–263.
7. Notabartolo D, Merlino JD, Smith AL, et al. Usefulness of the peak velocity difference by tissue Doppler imaging technique as an effective predictor of response to cardiac resynchronization therapy. *Am J Cardiol*. 2004;94:817–820.
8. Verbrugge FH, Verhaert D, Grieten L, et al. Revisiting diastolic filling time as mechanistic insight for response to cardiac resynchronization therapy. *Europace*. 2013;15(12):1747–1756.
9. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352(15):1539–1549.
10. Kron J, Aranda JM, Miles WM, et al. Benefit of cardiac resynchronization in elderly patients: results from the multicenter InSync randomized clinical evaluation (MIRACLE) and multicenter InSync ICD randomized clinical evaluation (MIRACLE-ICD) trials. *J Intervent Card Electrophysiol*. 2009;25(2):91–96.

11. Emkanjoo ZEM, Mohammed Hadi N, Alizadeh A, et al. Frequency of inter- and intraventricular dyssynchrony in patients with heart failure according to QRS width. *Europace*. 2007;9:1171–1176.
12. Verbrugge FH, Verhaert D, Grieten L, et al. Revisiting diastolic filling time as mechanistic insight for response to cardiac resynchronization therapy. *Europace*. 2013;15(12):1747–1756.
13. Thomas DE, Yousef ZR, Fraser AG. A critical comparison of echocardiographic measurements used for optimizing cardiac resynchronization therapy: stroke distance is best. *Eur J Heart Fail*. 2009;11(8):779–788.
14. Sakamaki F, Seo Y, Atsumi A, Yamamoto M, et al. Novel dyssynchrony evaluation by M-mode imaging in left bundle branch block and the application to predict responses for cardiac resynchronization therapy. *J Cardiol Suppl*. 2014;64(3):199–206.