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

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A B S T R A C T — 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 in predicting subsequent benefit of CRT. One third of patients with prolonged QRS do not exhibit intra-left ventricular (LV) dyssynchrony, 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 hospital for CRT implantation based on the following conventional indication: NYHA 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 (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 was classified as echocardiographic or clinical as follows:

Echocardiographic responders (at least 2 of the following):
1. >15% reduction in LV end-systolic volume (LVESV)
2. Improvement in left ventricular ejection fraction (LVEF) ≥ 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

Clinical responders
1. Improvement by ≥ 1 NYHA functional class
2. Improvement by ≥ 10% in 6MWD

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

### Table 1

#### Baseline demographics and medications.

| Parameter | Criteria for dyssynchrony | Criteria for response | Methodology |
|-----------|---------------------------|------------------------|-------------|
| 1         | LVEF - Visual - Simpsons Method | Increase in LVEF by ≥ 10% | Apical 4 chamber view |
| 2         | LVDD and LVIDs           |                         | PLAX view on M-mode, at level of tips of mitral leaflets |
| 3         | EDV and ESV              | Decrease in LDV by 15%  | Assessed in 4 apical chamber view by Simpson’s technique |
| 4         | Conventional M-mode: Septal-Post delay |Delay < 100 ms| SAX at mid-ventricular level |
| 5         | Conventional M-mode: Ant-Post delay |Delay < 100 ms| SAX at mid-ventricular level Septum @ 10 o’clock Lateral @ 4 o’clock Posterior @ 6 o’clock |
| 6         | Anatomic MMMode (AMM): Septal to Lateral wall delay (SLWD); Septal to Posterior wall delay (SPWD) |<40% | Apical 4 chamber with PW Doppler and ECG |
| 7         | Diamt T/LRR               | >50%                   | Apical 4 chamber with the help of PW on mitral valve inflow; MV VT area traced manually |
| 9         | Radial Strain             | ≥ 100 ms               | Measured with the help of Qlab software |

### Table 2

#### Dyssynchrony parameters.

| Parameter | Criteria for dyssynchrony | Criteria for response | Methodology |
|-----------|---------------------------|------------------------|-------------|
| 1         | LVEF - Visual - Simpsons Method | Increase in LVEF by ≥ 10% | Apical 4 chamber view |
| 2         | LVDD and LVIDs           |                         | PLAX view on M-mode, at level of tips of mitral leaflets |
| 3         | EDV and ESV              | Decrease in LDV by 15%  | Assessed in 4 apical chamber view by Simpson’s technique |
| 4         | Conventional M-mode: Septal-Post delay |Delay < 100 ms| SAX at mid-ventricular level |
| 5         | Conventional M-mode: Ant-Post delay |Delay < 100 ms| SAX at mid-ventricular level Septum @ 10 o’clock Lateral @ 4 o’clock Posterior @ 6 o’clock |
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| 7         | Diamt T/LRR               | >50%                   | Apical 4 chamber with the help of PW on mitral valve inflow; MV VT area traced manually |
| 9         | Radial Strain             | ≥ 100 ms               | Measured with the help of Qlab software |

### Table 3

#### Echocardiographic Parameters pre-CRT, post-CRT and follow up.

| Parameter | Pre-CRT (n = 33) | Post-CRT (n = 33) | Follow up (n = 33) | p-value (T-test) |
|-----------|------------------|------------------|-------------------|-----------------|
| 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           |                 |
| LVDD      | 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    | 0.4 ± 0.07       | 0.4 ± 0.08       | 1.8 ± 0.76        | 0.25462         |
| Mitral VTI| 162.2 ± 3.6      | 16.4 ± 4.8       | 18.1 ± 5.6        | 0.10583         |
| VTI/RR    | 0.0195 ± 0.006   | 0.0193 ± 0.0043  | 0.0193 ± 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 L | 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 ± 190.0     | 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         |

* 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 LVEDV values
b) The mean mitral DFT values
c) The mean mitral VTI values
d) The MVVTI/RR values
e) The SAX-Mid A-P values
f) The SAX-Mid S-L values
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 CRT indicate that none of the traditional selection criteria (NYHA class III–IV, LV ejection fraction ≤0.35 and QRS duration ≥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.5,10 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 al12 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 al13 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 (SLD) delays, unlike conventional M-mode which only measures anterior-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 al14 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.

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