Electrical remodelling and response following cardiac resynchronization therapy: A novel analysis of intracardiac electrogram using a quadripolar lead

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Abstract
Background: Cardiac resynchronization therapy (CRT) improves morbidity and mortality in patients with heart failure. Although structural remodelling correlates with improved long-term outcomes, the role of electrical remodelling is poorly understood. This study aimed to evaluate electrical remodelling following CRT using a quadripolar left ventricular (LV) lead and to correlate this with structural remodelling.

Methods: Consecutive patients undergoing initial CRT implantation using a quadripolar LV lead were enrolled. Patients were followed up for 12 months. Twelve lead ECG, transthoracic echocardiogram, and evaluation of intracardiac electrograms (EGM) were performed. Measures included right and left ventricular lead intrinsic delay, RV-pacing to LV-sensing (RVp-LVs) delay, and LV-pacing to RV-sensing (LVp-RVs) delay. The electrical changes were then correlated with echocardiographic response to CRT, defined by ≥15% relative reduction in LVESV and ≥5% absolute improvement in EF on TTE. Activation sequence was determined using the quadripolar lead.

Results: Forty patients were enrolled. Mean intrinsic RV-LV EGM values decreased from 121.9 ± 14.7 ms to 109.1 ± 15.0 ms (P < .01), mean RVp-LVs EGM values from 146.7 ± 16.7 ms to 135.1 ± 13.1 ms, (P < .01), and mean LVp-RVs EGM values from 155.7 ± 18.1 ms to 144.2 ± 17.1 ms (P < .01). The improvement in intrinsic RV-LV EGM was 14.9 ± 8.5 ms in responders vs 8.9 ± 7.9 ms in nonresponders to CRT (P < .05). Changes in activation sequence did not correlate with CRT response.

Conclusions: This novel study used EGMs from a quadripolar LV lead to demonstrate electrical remodelling occurs following CRT. A nonsignificant trend suggests that electrical remodelling in CRT is greater in responders compared to nonresponders, although further study is needed.

KEYWORDS
artificial, cardiac pacing, cardiac resynchronization therapy, cardiac resynchronization therapy devices, echocardiography, heart failure
1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) is a proven and effective treatment in the management of patients with symptomatic heart failure despite medical optimization as reflected in the American Heart Association guidelines. However, nonresponder rates remain high and factors influencing response to CRT are poorly understood.

Resynchronization of ventricular contraction is the fundamental aim of CRT. The improvements in long-term outcomes correlate most strongly with structural remodelling. Indeed, response to CRT is often defined as a reduction in left ventricular end systolic volume (LVESV), left ventricular end diastolic diameter (LVEDD), and/or an improvement in ejection fraction (EF).

The importance of baseline electrical abnormalities in predicting response to CRT is well established. The presence of a left bundle branch block (LBBB) and a prolonged QRS duration consistently predict response to CRT. A degree of electrical remodelling following CRT, defined according to surface ECG criteria, has been described and has demonstrated nonsignificant trends toward correlation with anatomical remodelling and response to CRT. However, surface ECG is only a crude measure of electrical activation and conduction.

This novel study examined the nature of electrical remodelling following CRT using the intracardiac electograms (EGM) recorded from the quadripolar LV leads to quantify electrical remodelling and correlate with structural response to CRT.

2 | METHODS

Consecutive patients undergoing initial CRT implantation at a tertiary centre between 2012 and 2014 were evaluated. Patients with symptomatic heart failure New York Heart association (NYHA) class II-III symptoms, an EF < 35% with a QRSd ≥ 140 ms with a LBBB morphology were enrolled in the analysis. Patients with one or more of atrial fibrillation, right bundle branch block (RBBB), or a nonspecific interventricular conduction delay were excluded. Only patients successfully implanted with a quadripolar lead were included in the analysis.

Patients were assessed prior to implantation per our unit protocol. Prior to CRT implantation, all patients underwent baseline 12-lead ECG, transthoracic echocardiography (TTE), and assessment of NYHA functional class. Patients were enrolled after informed consent.

Figure 1 shows postprocedural plain radiographs of a CRT-defibrillator in situ. The 4 electrodes on the quadripolar lead are labelled as D1, M2, M3, and P4.

2.1 | Echocardiography

TTE examination was performed using the Vivid 7 & 9 (General Electric). Left ventricular end diastolic volume (LVEDV), LV end systolic volume (LVESV), and LV EF were assessed using the modified Simpson’s biplane method.

2.2 | Implant procedure

Standard trans-venous CRT implantation was performed under general anesthesia or using sedation with local anesthesia. The RV lead was positioned in the mid septum as per our usual practice and was defined by fluoroscopic imaging in the anterior-posterior (AP) and left anterior oblique (LAO) 40° view. The right atrial (RA) lead was positioned in the RA septum or RA appendage as per convention. The coronary sinus was cannulated using standard sheaths with guidewire, and a venogram of the coronary vein tributaries was obtained. A St Jude Medical Quartet quadripolar LV lead was used in all patients. As per our unit policy, we targeted the lead to anatomically delayed segments as identified by the preoperative TTE and the final position was determined according to local EGM measures. Lead was repositioned if the pacing threshold at targeted electrode was > 2.5V at 0.5 ms or if there was phrenic nerve stimulation at less than twice the local capture threshold.
2.3 | Intracardiac electrograms

EGM (Figure 2A-B) were assessed using the standard programmer of respective device companies. The intrinsic electrogram delay was measured during native conduction in sinus rhythm at each of the 4 LV electrodes from the earliest sensed EGM signal on the RV channel to the local unipolar EGM at each electrode of the LV lead. The RV paced delay (RVp-LVs) was measured with RV-only bipolar pacing, at twice the recorded threshold, from the local pacing marker to the earliest unipolar EGM at each of the electrodes. The LV paced delay (LVp-RVs) was measured from the pacing marker to the earliest local EGM on the RV lead channel with LV-only unipolar pacing from each LV electrode. Data will be presented as the “mean” of four measurements from each LV electrode and the “maximum” from within that group. The initial and follow-up EGM measurements were made by the same team of physicians and pacing technicians. The measurements were performed independently by two observers with considerable experience in measuring intracardiac EGMs from previous studies. The observers were blinded to the echocardiographic findings at the time of measuring EGMs. We have previously determined an intraobserver variability of < 5%. 10

2.4 | Activation sequence

Using the quadripolar lead, the left ventricular activation sequence was then categorized into (i) sequential proximal to distal (Sq P-D), (ii) sequential distal to proximal (Sq D-P), or (iii) nonsequential (non-Sq). It was defined as Sq P-D when the earliest activation was in the proximal pole and the latest activation in the distal pole (see Figure 1). Sq D-P when the earliest activation was in the distal pole and the latest activation in the proximal pole and non-Sq when the pattern did not follow the above descriptions. A change in activation sequence was defined as any change between the above three conditions between baseline and 12-month follow-up. An example of a changing activation sequence is provided in Table 1.

2.5 | Follow-up

TTE, ECG, and EGM measures were performed immediately following implant and 12-months post implant which was incorporated into our routine follow-up.

2.6 | Definition of CRT response

Response to CRT was defined by ≥15% relative reduction in LVESV and ≥ 5% absolute improvement in EF on TTE.

2.7 | Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Interobserver variability and correlation between 2 independent variables were calculated using the Pearson’s correlation coefficient. P values were calculated using a heteroscedastic, one- (for results measured at 12-month follow-up) or two (for results measured at baseline)-tailed Student’s t test or Fischer’s exact t test. One-tailed tests were used for variables measured after the CRT intervention and two-tailed tests used for variables measured prior to CRT intervention. The paired t test was used to compare changes in variables across time. Statistical significance was defined as P < .05.

3 | RESULTS

A total of 67 patients underwent CRT of which 43 patients were enrolled in this study. Patients were excluded due to non-LBBB morphology (13), atrial fibrillation (5), QRS duration < 145 ms (3), non-Quartet technology (2), and inability to pace and or sense from all 4 electrodes of the LV lead (2). Forty (93%) patients completed follow-up, one patient failed to attend follow-up, and two patients were excluded as they underwent AV nodal ablation prior to completion of the protocol. Mean age was 65 ± 12.9 years with 70% being men. The mean QRSd was 154.1 ± 8.1 ms with 55% nonischaemic etiology.

3.1 | Response to CRT

The mean EF improved from 24.1 ± 6.1% to 32.7 ± 9.0% (P < .01) after implantation, and the mean LVESV was reduced from 167.0 ± 62.1 mL to 133.6 ± 50.2 mL (P < .01). Twenty-six (65%) patients were considered responders as defined using both echocardiographic measures. Thirty-two (80%) patients had a response to one echo measure, 29 (72.5%) had a LVESV ≥15% relative reduction, and 29 (72.5%) had a LV EF ≥ 5% absolute improvement.

Responders were more symptomatic at baseline (NYHA 2.71 vs 2.07) and younger (62.0 vs 70.4 years). There was no significant difference at baseline with respect to etiology, QRSd, EF, LVEDD, or LSES, Table 2.

3.2 | Electrical remodelling

There was a significant reduction in the EGM parameters between baseline and 12 months during both paced and intrinsic conduction, Table 3. The mean EGM values decreased from 121.9 ± 14.7 ms to 109.1 ± 15.0 ms for Int RV-LV (P < .01), from 146.7 ± 16.7 ms to 135.1 ± 13.1 ms for RVp-LVs (P < .01), and from 155.7 ± 18.1 ms to 144.2 ± 17.1 ms for LVp-RVs (P < .01).

3.3 | Electrical remodelling and echocardiographic response

The changes in EGM values were larger for echocardiographic responders, Table 4. The mean EGM reduction during intrinsic rhythm of responders was 14.9 ± 8.5 ms as compared with 8.9 ± 7.9 ms, for nonresponders (P = .02). The observed reduction in RV paced delay (13.1 ± 8.6 ms compared to 8.5 ± 8.3 ms, P = .06) and LV paced delay (13.4 ± 7.4 ms compared to...
FIGURE 2  Intracardiac electrograms showing: A, int RV-LV; B, LVp-RVs
**TABLE 1** Int RV-LV (ms) for each of the 4 electrodes (See Figure 2) at implant and at 12-month follow-up for a particular patient. This patient demonstrates a change in activation sequence from sequential distal to proximal to nonsequential.

| LV electrode | Int RV-LV at implant (ms) | Int RV-LV at follow-up (ms) |
|--------------|---------------------------|----------------------------|
| D1           | 170                       | 107                        |
| M2           | 177                       | 131                        |
| M3           | 178                       | 145                        |
| P4           | 192                       | 127                        |

**TABLE 2** Patient characteristics divided according to CRT response, mean ± SD.

| All patients n = 40 | Responder n = 26 | Nonresponder n = 14 |
|----------------------|------------------|---------------------|
| NYHA Class           |                  |                     |
| Class I              | 2.47 ± 0.76      | 2.71 ± 0.69         |
| Class II             | 6.50 ± 13.0      | 62.0 ± 13.7         |
| Class III            | 5.00 ± 10.0      | 70.4 ± 9.67         |
| Age (years)          |                  |                     |
| Male                 | 28 (70)          | 16 (62)             |
| Female               | 12 (30)          | 10 (38)             |
| QRSd (ms)            |                  |                     |
| Intrinsic            | 154.4 ± 8.1      | 155.0 ± 8.4         | 153.2 ± 7.8 |
| Etiology (%)         |                  |                     |
| Ischaemic            | 18 (45)          | 9 (41)              |
| Nonischaemic         | 22 (55)          | 17 (59)             |
| EF Pre-CRT (%)       | 24.10 ± 6.1      | 23.81 ± 5.8         |
| EF Post-CRT (%)      | 32.73 ± 9.0      | 36.31 ± 7.4         |
| Change EF (%)        | 8.63 ± 8.3       | 12.50 ± 7.6         |
| LVEDD Pre (mL)       | 65.75 ± 4.9      | 66.27 ± 4.9         |
| LVEDD Post (mL)      | 58.75 ± 6.4      | 56.42 ± 5.6         |
| Change LVEDD (%)     | −10.60 ± 7.6     | −14.87 ± 5.4        |
| LVESE Pre-CRT (mL)   | 167.6 ± 62       | 173.8 ± 65          |
| LVESE 12 mo (mL)     | 133.6 ± 50       | 129.2 ± 49          |
| Change LVESE 12 mo (%)| −19.49 ± 11    | −25.37 ± 6.7        |

**TABLE 3** EGM values (ms), mean ± SD

|                      | Implant | 12 mo | Reduction | P value for reduction |
|----------------------|---------|-------|-----------|-----------------------|
| Intrinsic RV-LV      |         |       |           |                       |
| Mean                 | 121.9 ± 14.7 | 109.1 ± 15.0 | 12.8 ± 8.7 | <.01                 |
| Maximum              | 129.4 ± 15.5 | 116.5 ± 16.1 | 12.9 ± 10.0 | <.01                 |
| RVp-LVs              |         |       |           |                       |
| Mean                 | 146.7 ± 16.7 | 135.1 ± 13.1 | 11.5 ± 8.7 | <.01                 |
| Maximum              | 154.2 ± 17.1 | 141.9 ± 12.7 | 12.3 ± 9.5 | <.01                 |
| LVp-RVs              |         |       |           |                       |
| Mean                 | 155.7 ± 18.1 | 144.2 ± 17.1 | 11.5 ± 9.2 | <.01                 |
| Maximum              | 171.4 ± 20.4 | 157.8 ± 16.3 | 13.6 ± 10.4 | <.01                 |

**TABLE 4** Reduction in mean EGM values (ms) from implantation to 12 mo, divided according to CRT response

|                    | Responders | Nonresponders | P value |
|--------------------|------------|---------------|---------|
| Intrinsic RV-LV    | 14.9 ± 8.5 | 8.9 ± 7.9     | <.02    |
| RVp-LVs            | 13.1 ± 8.6 | 8.5 ± 8.3     | <.06    |
| LVp-RVs            | 13.4 ± 7.4 | 9.1 ± 8.6     | <.05    |

Mean ± SD.

9.1 ± 8.6 ms, P = .05 was also greater for responders compared to nonresponders, although results just failed to reach statistical significance.

3.4 | QRSd

The mean QRSd reduced from 154.1 ± 8.1 ms to 138.7 ± 15.1 ms, P < .05. There was no difference in the reduction in QRSd between responders (17.5 ms) and nonresponders (16.1 ms). No correlation was found between reduction in intrinsic QRSd and reduction in EGM measures, $r^2 = .03$.

3.5 | Activation sequence

Intrinsic activation sequence changed in 16 of 40 (40%) patients during the 12-month follow-up. Twelve of 26 (46%) responders and 4 of 14 (29%) nonresponders had a change in intrinsic activation sequence over 12 months ($P = .145$). Among those with a change in activation sequence, LVESE improved in 18.5% compared to 16.8% ($P = .28$) for those without. Regarding EF, those with a change in activation sequence had an improvement of 11% compared to 6% ($P = .10$) for those without a change in activation sequence.

4 | DISCUSSION

CRT may alter electrical activation to improve mechanical function and in turn, facilitate remodelling. This study suggests that CRT may also improve electrical delays that are present in these patients. The major finding of this study is that electrical remodelling, as measured using intracardiac EGM, occurs following CRT. The electrical remodelling appears to be more pronounced in responders to CRT compared with nonresponders, although results did not quite achieve statistical significance. A nonsignificant trend emerged that these changes appear to be nonuniform as we observed a change in electrical activation sequence over time in some patients.

4.1 | Remodelling

The clinical benefits of CRT are well established. Improvement in ejection fraction, left ventricular dimensions, and degree of mitral regurgitation have all been demonstrated. Degree of anatomical remodelling has correlated with the clinical improvement measured by symptoms, 6-minute walk distance or VO2, and improvement
in physical activity has correlated with survival. This study demonstrates that electrical remodelling also occurs following CRT. More importantly, the degree of electrical remodelling appears more pronounced in CRT responders.

Previous evidence for electrical remodelling in CRT has relied upon a correlation between clinical response and a reduction in intrinsic QRS duration. This unique analysis demonstrates electrical remodelling both in intrinsic and in paced rhythms using intracardiac EGMs which are easily accessible and reproducible.

The definition of baseline electrical delays in patients as measured by ECG and EGM has consistently been shown to predict response to CRT. Given the importance of baseline electrical abnormalities in predicting response to CRT, the correlation between improvement in electrical delays and response to CRT was expected. Intrinsic electrical delays improved by more than 10 ms overall, but the improvement was greatest in the patients who had a structural response to CRT.

Previous studies using surface ECGs have demonstrated improvement in QRS duration following CRT but these results have been inconsistent. We found an overall reduction in QRSd in patients following CRT but no significant difference in QRSd between responders and nonresponders was seen. Improvement in QRSd did not translate to reduction in EGM measures or vice versa.

We did not observe statistically significant evidence of an association between changes in activation sequence and structural CRT response. However, we have presented a novel and reproducible method for the measurement of electrical activation sequence using a quadripolar lead. The strength of this approach is that it is easily reproducible and requires no further invasive testing at the time of implantation or follow-up, but is limited by poor spatial resolution as it relies upon 4 points to model a complex 3d waveform.

4.2 Clinical relevance

Optimal delivery of CRT is in part achieved by programming the electrical delays between the right and left ventricular leads to optimize synchronization of ventricular contraction. We have previously demonstrated the variability in optimal programming parameters over time and that a quadripolar lead provides additional pacing options compared to bipolar and tripolar equivalents. This study adds further to our understanding of the variability between individuals and the need for regular and ideally device-based alterations of RV-LV offsets. The variable improvement in electrical conduction in both intrinsic and paced rhythm may necessitate individualized changes in device programming to deliver optimal CRT for the best patient outcome.

4.3 Limitations

This is a single centre prospective study that has demonstrated electrical remodelling in a relatively small and homogenous population of patients undergoing CRT implantation. All patients were in sinus rhythm with a broad LBBB and had the LV lead implanted in an area of significant intrinsic electrical delay. Our inclusion criteria were deliberately more strict than American Heart Association guidelines as, given our small sample size, we sought to identify those patients in whom changes in the electrical substrate would be most obvious. The applicability of these results to a more heterogeneous population remains uncertain.

The definition of response to CRT is not uniform among published studies making comparison between studies problematic. Ideally, we would identify responders to CRT based on clinical echocardiographic and outcome criteria. This analysis used echo as the sole marker of response as we were primarily aiming to analyse the relationship between electrical and structural remodelling. The correlation between electrical remodelling and clinical outcomes remains uncertain.

Whilst the change in activation sequence and the nonuniform remodelling seen in this analysis suggests that electrical remodelling is evident, it is not possible to say these changes are not simply a reflection of reducing LV volumes. It may be that the electrical changes are subtler than we originally hypothesized and require a larger data set to clearly delineate. The significant improvement in electrical parameters in the patients who were echocardiographic responders and yet poor correlation between the degree of volumetric reduction and degree of electrical improvement supports the argument that both electrical and structural remodelling occur. A major limitation of our study is that statistical power was limited by its small sample size and certainly larger studies are needed to further investigate the trends we have identified. This particularly limits our ability to stratify by ischaemic or nonischaemic etiology and other clinical variables.

5 CONCLUSIONS

Electrical remodelling occurs after CRT during paced and intrinsic activation as measured through a quadripolar LV lead during 12-month follow-up. Although not statistically significant, electrical remodelling was more pronounced in CRT responders. The dynamic nature of the electrical remodelling suggests ongoing reevaluation in patients with CRT. The role of electrical remodelling as a therapeutic mechanism and independent predictor of clinical response will need ongoing evaluation.

CONFLICT OF INTEREST

DO has received research grants and speaker honoraria from Medtronic Inc and St Jude Medical. DF and HS have received fellow support from Medtronic Inc whilst involved in the research.

AUTHOR CONTRIBUTIONS

LT: data curation, formal analysis, writing—original draft preparation; DF: data curation, formal analysis, writing—original draft preparation, writing—review and editing; HS: data curation, formal analysis, writing
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