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Electrical remodelling post cardiac resynchronization therapy in patients with ischemic and non-ischemic heart failure

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ABSTRACT

Background: The beneficial effects of cardiac resynchronization therapy (CRT) in heart failure are largely considered to be due to improved mechanical contractility. The contributory role of electrical remodelling is less clear. We sought to evaluate the impact of electrical remodelling in these patients.

Methods: 33 patients with conventional indications for CRT and with ischemic (ICM) (n = 17) and non-ischemic (NICM) (n = 16) aetiologies for heart failure were prospectively recruited. Functional parameters of peak exercise oxygen consumption (VO_2max) and Minnesota quality of life (QOL) score, echocardiographic measures of LV functions and parameters of electrical remodelling, e.g. intrinsic QRS duration (iQRSD), intracardiac conduction times of LV pacing to RV electrocardiogram (LVp-RVegm), were measured at CRT implant and after 6 months.

Results: Only two electrical parameters predicted functional or symptomatic improvement. LVp-RVegm reduction significantly correlated with improvement in VO_2max ($r = -0.42$, $p = 0.03$ while reduction in iQRSD significantly correlated with improvement in QOL score ($r = 0.39$, $p = 0.04$). The extent of changes in LVp-RVegm and iQRSD was significantly greater in NICM than in ICM patients ($p = 0.017$ and $p = 0.042$ for heterogeneity). There was also significant differential impact on QOL score in the NICM relative to the ICM group ($p = 0.003$) but none with VO_2max. On multivariate analysis, only non-ischemic aetiology was a significant determinant of reduction in iQRSD.

Conclusion: CRT induces potentially beneficial reduction in LVp-RVegm and iQRSD, which are seen selectively in NICM rather than ICM patients. The extent of improvement in these markers is associated with some functional and symptomatic measures of CRT efficacy.

Introduction

Results from previous landmark studies have clearly shown that cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with chronic systolic heart failure and associated prolonged QRS duration [1,2]. To date, prolonged QRS duration, especially of left bundle branch block morphology, remains the best predictor of response to CRT [3]. Indeed, in patients with evidence of mechanical dyssynchrony on echocardiogram but with narrow QRS duration, CRT is futile and may be associated with harm [4,5]. In spite of this, the benefit of CRT on improved left ventricular volume and systolic function has been considered to be largely mediated by reversal of adverse left ventricular mechanical remodelling [6–8] rather than through positive electrical remodelling.

Although there are limited data reporting changes in individual electrical parameters following CRT, the majority have focused on relatively simple tools such as intrinsic QRS complex duration and morphology and QT dispersion [9–11] and have yielded inconsistent results [9]. The effects of CRT on other parameters of electrical remodelling are not well characterized, nor are the relationships between electrical remodelling and changes to functional status and mechanical function.

Furthermore, it is well recognized that CRT is associated with reduction in the occurrence of ventricular arrhythmias, especially in patients who achieve echocardiographic improvement in LV function and volumes [10]. Although the mechanism is at present unknown, positive electrical remodelling may play a role due to alterations in intracardiac electrical conduction and refractoriness.

Finally, whether electrical remodelling plays a role in the observation that patients with non-ischemic aetiology of heart failure (NICM) have greater improvement in left ventricular mechanical remodelling following CRT compared to those with an ischemic basis of heart failure (ICM) [11] remains to be fully explored. There are significant differences

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between patients with NICM and ICM. Functional LBBB rather than fixed block has been noted to be more prevalent in patients with NICM than in those with ICM [12], perhaps making patients with NICM more amenable to improvement with CRT in electrical parameters and consequently to improvement in mechanical function than those with ICM.

In this study, we prospectively evaluated changes in intra-cardiac electrical parameters following CRT, utilizing markers of excitability and local and global electrical conduction in patients with both ischemic and non-ischemic aetiologies of heart failure.

Objectives

1. To evaluate the effects of CRT on reversal of electrical remodelling.
2. To test the null hypothesis that extent of reversal in electrical remodelling is independent of a history of ischemic heart disease.
3. To test the hypothesis that extent of electrical remodelling predicts functional and/or symptomatic improvement post CRT.

Methods

Patient selection

33 patients with either ICM (n = 17), (patients with documented prior myocardial infarction based on previous history, echocardiographic regional wall motion abnormality consistent with single or multi-vessel arterial territory (ies), and or abnormal coronary angiogram) or NICM (n = 16) (patients with no prior myocardial infarction and whose coronary angiogram have shown no significant coronary artery disease) and conventional indications for CRT [13] were recruited from three hospital sites and prospectively evaluated at baseline and 6 months after insertion of a CRT device. Baseline functional parameters of VO_2max and quality of life assessment (utilizing the Minnesota Living with Heart Failure Questionnaire) were performed two weeks or less prior to the implantation of CRT and baseline electrical parameters were performed immediately after implantation of CRT. All parameters were examined for the total cohort and then for the pre-specified groups of ICM and NICM patients.

Functional status assessment

Cardio-pulmonary exercise testing

Cardio-pulmonary exercise testing (CPET) was performed according to established guidelines [14] Briefly, a bicycle ergometer (Model: ergoline/100/200 GmbH, Germany) and linked to ExpAir Medisoft S.A Belgique 1.31.02 software was utilized in all cases. Before performing each test, the equipment was calibrated both for airflow or volume, including low and high flows (with calculated volumes within ±3%) using a 3Litre syringe, and also for gases with carbon dioxide set at 4% and oxygen at 20%. A semi- automated progressive incremental (ramp) protocol, in which the pre-test was set at 0 watts, while the workload started from 10watts and increased by 10 watts every minute, was used. Patients pedalled for a minute on the pre test setting of 0 watts before loading commenced. They were encouraged to exercise as long as possible, ideally for up to 8 to 12 min, and especially aiming to achieve a respiratory exchange ratio (RER) of 1 and above, with cycling rate kept at 60–70 rpm. Volitional exhaustion was the usual endpoint although exercise was terminated if a patient developed chest pain, acute ischemic changes on the ECG or hypotension. After unloading, the patient pedalled for a further 1 min. Measurements of oxygen consumption (VO_2) carbon dioxide output (VCO_2) ventilator equivalent, (VE) and RER were automatically acquired and finally averaged and displayed at 10-s intervals. The highest reading of the three last averages at peak exercise was chosen as the VO_2 max.

Quality of life score

The self-administered Minnesota Living with Heart Failure Questionnaire [15] assessed quality of life score with higher scores indicating lower functional status.

Measures of electrical remodelling

Parameters utilized included the intrinsic QRS duration as an overall marker of global electrical dyssynchrony, left ventricular pacing to the onset of right ventricular intra-cardiac electrocardiogram (LVp-RVegm), right ventricular pacing to the onset of left.

ventricular intra-cardiac electrocardiogram (RVp-LVegm), calculations of Q-LVegm and left ventricular intra-cardiac electrocardiogram to the end of QRS complex (LVegm-QRSend) as markers of interventricular electrical conduction times.

As regards specific methodology:

Intrinsic QRS duration

At baseline, intrinsic QRS duration (iQRSD) was measured from the onset of the initial deflection of the QRS complex to the end of the terminal deflection using lead II in all cases at a sweep speed of 50 mm/s. At 6 months, pacing was temporarily turned off for 120 s to enable repeat measurement of intrinsic QRS duration using lead II at a sweep speed of 50 mm/s. Lead II was utilized in the measurement of intrinsic QRS duration in all cases for consistency and also because of the left ventricular apical orientation of lead II vector.

Left ventricular pacing to right ventricular intra-cardiac electrocardiogram (LVp-RVegm)

Immediately after insertion of CRT device, the conduction time from the onset of left ventricular-only pacing to the onset of the right ventricular intra-cardiac electrocardiogram was measured for each patient in milliseconds. For this, pacing was temporarily performed from the left ventricular lead only in VVI mode and at 100 paces per minute for 30 s. LVp-RVegm was taken from the last paced 3 beats, which ever was longest.

Measurements were performed at sweep speed of 100 mm/s. This measurement was repeated 6 months afterwards. No patient had any re-manipulation of the left ventricular pacing lead or change in pacing vectors.

Right ventricular pacing to left ventricular intracardiac electrocardiogram (RVp-LVegm)

a. Conduction time from the onset of right ventricular pacing to the onset of left ventricular intracardiac electrocardiogram was measured at a sweep speed of 100 mm/s with the right ventricle paced at 100 paces per minute in VVI mode for 30 s. RVp-LVegm was taken from the last paced 3 beats, which ever was longest. Measurements were performed at sweep speed of 100 mm/s.

Measurement was performed immediately after CRT insertion and was repeated 6 months afterwards.

Q-LVegm

This measures the interval between the onset of QRS and the onset of left ventricular intra-cardiac electrocardiogram. Lead II was used to measure the onset of QRS.

RVegm-LVegm

This is the difference between the onset of right ventricular intracardiac electrocardiogram and the onset of left ventricular intracardiac electrocardiogram. This denotes the timing difference in the spontaneous depolarization of the right and the left ventricles.

Left ventricular intra-cardiac electrocardiogram to the end of QRS complex (LVegm-QRSend)

This was calculated as the difference between the intrinsic QRS duration and Q-LVegm.

None of the patients had any of the leads repositioned during the study period thereby ensuring constant landmarks for the measurements. The LV leads were inserted at the discretion of the implanter aiming at the lateral or posterolateral coronary sinus branch. Leads were not positioned in areas where thresholds were high or areas of non-capture.

Echocardiographic measurements

All echocardiographic measurements were performed according to the American Society of Echocardiography guidelines [14]. A Phillips echocardiogram machine model iE33, 2009, Bothell WA, 98041 USA was used for image acquisition, and analyses were performed using Echopac Software Only BT 11 Version 113, 2013 General Electric Co. Measurements included left ventricular end-diastolic and end-systolic volumes, from which ejection fraction was calculated with Simpson's rule for biplane evaluation. Inter-ventricular mechanical delay (IVMD) was used as a measure of mechanical dyssynchrony. IVMD was calculated as the difference between the aortic pre- ejection time, measured from the onset of QRS complex and the onset of aortic pulsed-wave Doppler velocity in the apical 5-chamberer view and that of the pulmonary pre-ejection time, measured from the onset of QRS complex and the onset of pulmonary artery pulsed wave velocity in the parasternal short axis view.

The study complies with the *Declaration of Helsinki* and the Ethics and Human Research Committee of The Queen Elizabeth Hospital granted approval for the study. All participants provided prior written informed consent.

Statistical analyses

All data are expressed as mean ± SD unless stated otherwise. Interval changes in functional and electrophysiological parameters were assessed using paired *t*-test for normally distributed variables, and Wilcoxon matched-pairs signed rank test for non-parametric data. Each patient served as his/her control. Interactions between changes in functional status and changes in electrical parameters were correlated using Pearson correlation coefficients for normally distributed data and Spearman correlation for non-parametric data. Categorical variables were analysed with chi-square and Fisher's exact test. A two-tailed *P* value <0.05 was considered statistically significant.

All data were analysed with Prism 7 for Mac OS X version 6.0 h October 2016 apart from backward stepwise multivariate analysis performed on SPSS version 11.8.2, year 2013.

Results

Baseline characteristic

Table 1 shows the patients' baseline demographics. 17 patients (52%) had underlying ischemic aetiology of heart failure and all patients were extensively treated medically. The NICM group had higher baseline LVEF of 0.33 ± 0.06 versus 0.26 ± 0.04, $p = 0.001$, and significantly lower left ventricular volumes, while diabetes and statin therapy were more frequent among the ICM patients. The mean baseline intrinsic QRS duration was 158 ± 27.2 ms. There were no significant differences in baseline electrical parameters in both groups. No patient had right bundle branch block on the ECG, two had intra-ventricular conduction delay, two were paced and the rest had LBBB. Of the initial 33 patients, 1 died a month after CRT insertion and 3 did not return for follow-up.

Changes in mechanical and clinical parameters

At 6 months, there were significant improvements in LVEF from 31 ± 6 to 38 ± 10% ($p < 0.001$), in mechanical dyssynchrony as assessed with IVMD 43.6 ± 44.6 to 19.9 ± 33.9 ms ($p = 0.012$) and in symptomatic status as measured with the QOL score 40.7 ± 25.4 to 22.9 ± 22.3 ($p = 0.001$) in the whole cohort (Table 2). Notably, although at baseline the NICM group had better LV systolic function than the ICM group, at 6 months post CRT insertion, there were significant improvements in LVEF and LVESV in both groups and no significant differences between groups for LVEF or LVESV changes.

Changes in electrical parameters

In terms of electrical parameters, at 6 months, there was a trend towards reduction in intrinsic QRS duration in the whole cohort (159 ± 23.7 to 148 ± 29.4 ms, $p = 0.082$) and this was driven by significant reduction in iQRSD in NICM patients (165.4 ± 20.3 to 140.5 ± 28.6 ms, $p = 0.012$) (Fig. 1). There was no significant change in iQRSD in the ICM cohort from 153 ± 25.6 to 154 ± 28.4 ms, $p = 0.81$. Consistent with these data, the decrease in iQRSD in NICM patients was statistically greater than that in the ICM group ($p = 0.017$).

A similar pattern of results was found with the electrophysiological parameter of LVp-RVegm. In the whole cohort, there was significant reduction in LVp-RVegm from 116.7 ± 44.5 to 97.0 ± 45.0 ms ($p = 0.019$) (Fig. 2A) and this was driven by the NICM group (121 ± 31.4 to 86.4 ± 29.0 ms, $p = 0.005$) with no significant change in the ICM group (112 ± 56.2 to 109 ± 56.5 ms, $p = 0.76$). The between-group difference was also statistically significant ($p = 0.042$). For LVegm-QRSend calculations, there was significant reduction in the whole cohort from 77.5 ± 53.3 to 53.9 ± 35.5 ms, $p = 0.024$ (Fig. 2B) and this was somewhat more marked in the NICM (81.5 ± 60.4 to 48.6 ± 44.3 ms,) than in the ICM group (70.6 ± 51.6 to 63.5 ± 30.9 ms), none of these differences reached statistical significance.

No significant change was observed in RVp-LVegm at 6 months in the whole cohort (86.9 ± 39.6 to 93.3 ms, $p = 0.30$) and no significant change in RVegm-LVegm. These data are shown in Table 3.

A positive correlation was observed between change in iQRSD and change in LVegm-QRSend (Fig. 2D) but with no significant change in Q-LVegm at 6 months, (Fig. 2C). Although there was no significant improvement in VO_2 max at six months, there was a significant negative correlation in individual patients between change in VO_2 max and LVp-RVegm ($r = -0.42$, $p = 0.035$). There was also significant positive correlation between changes in QOL score and those in the iQRSD ($r = 0.39$, $p = 0.04$ Fig. 3A/B). We have nonetheless found no significant correlation between changes in LVp-RVegm and those of QOL score ($r = 0.24$, $p = 0.20$). There was also no significant correlation between changes in iQRSD and those of VO_2max ($r = -0.06$, $p = 0.76$).

Importantly, there was no significant correlation ($r = 0.18$, $p = 0.37$) between extent of electrical remodelling as measured by changes in iQRSD and that of mechanical remodelling, as measured by changes in IVMD.

Univariate correlates of reduction in intrinsic QRS complex duration.

On univariate analysis, lower baseline LVEDV and lower baseline LVESV were significantly associated with subsequent reduction in iQRSD, ($r = -0.43$, $p = 0.037$ and $r = -0.40$, $p = 0.049$ respectively). Baseline LVEF however, was not significantly associated with subsequent reduction in iQRSD ($r = 0.20$, $p = 0.32$). In spite of this finding, neither changes in LVEDV nor changes in LVESV or in LVEF were significantly associated with changes or reduction in iQRSD. Also, there was no significant association between age or the presence of diabetes with subsequent changes in iQRSD ($r = 0.03$, $p = 0.87$ and r = 0.03; $p = 0.89$ respectively). On the other hand, female gender and non-ischemic aetiology were significantly associated with subsequent reduction in iQRSD, ($r = 0.41$, $p = 0.031$ and $r = 0.42$, $p = 0.028$ respectively). These univariate correlates are shown in Table 4.

Table 1
Baseline characteristics of patients
Normally distributed data are mean ± SD; skewed data are expressed as median values and interquartile values.

	ALL (n = 33)	ICM (n = 17)	NICM (n = 16)	Unpaired t –test, *p*-value
Age (years)	71.2 ± 9.7	71.8 ± 10.2	71 (68.3–77.5)	0.64
Female, n (%)	10 (30.3)	3 (17.6)	7 (43.7)	0.10
BMI (kg/m^2)	29.3 ± 6.1	28 ± 6.45	30.7 ± 5.6	0.21
Comorbidities				
• Hypertension, n (%)	21 (64)	12 (70.5)	9 (56.2)	0.39
• Diabetes, n (%)	14 (42)	10 (58.8)	4 (25)	0.04
• Atrial fibrillation, n (%)	5 (15)	2 (11.7)	3 (18.7)	0.57
• eGFR (ml/min/1.73m^2)	56.2 (21.9)	53.1 (22.9)	59.7 (21.0)	0.39
Medications				
• ACE inhibitor	22 (67)	11 (64.7)	11 (68.7)	>0.99
• Angiotensin receptor blocker	8 (24)	5 (29.4)	3 (18.7)	0.68
• Beta blocker	25 (76)	13 (76.4)	12 (75.0)	>0.99
• Aldosterone antagonist	18 (55)	8 (47.0)	10 (62.5)	0.49
• Digoxin	9 (27)	4 (23.5)	5 (31.2)	0.61
• Furosemide	24 (73)	13 (76.4)	11 (68.7)	0.70
• Statin	18 (55)	13 (76.4)	5 (31.2)	0.01
• Aspirin	17 (52)	10 (58.8)	7 (43.7)	0.49
• Amiodarone	2 (6.0)	2 (11.7)	0 (0.0)	0.48
Clinical assessment				
Systolic BP (mmHg)	126 ± 17.1	125 ± 18.6	130 ± 16.8	0.44
Diastolic BP (mmHg)	71.2 ± 9.2	69.3 ± 9.0	73.8 ± 8.9	0.16
Heart rate (bpm)	69 ± 13.6	70.4 ± 11.6	67.5 ± 15.7	0.54
VO_2max (ml/min/kg)	13.8 ± 4.7	12.0 ± 4.0	15 ± 4.7	0.07
QOL score	41.9 ± 25.6	45.6 ± 26.0	38 ± 25.5	0.40
Ventricular function				
LVESV (ml)	137 ± 55.3	166 ± 53.0	108 ± 42.8	0.002
LVEDV (ml)	193 ± 67.4	224 ± 64.5	161 ± 55.9	0.006
EF (%)	29.8 ± 6.1	26 ± 4.0	33 ± 6.0	0.001
IVMD (ms)	43.9 ± 44.0	34.1 ± 45.7	53.0 ± 41.7	0.24
Electrical parameters				
iQRSD (ms)	158 ± 27.2	156 ± 24.9	161 ± 29.6	0.62
LVp-RVegm (ms)	118 ± 43.3	115 ± 52.4	121 ± 31.4	0.69
RVp-LVegm (ms)	88.5 ± 38.6	96.8 ± 39.5	79.2 ± 36.7	0.20
LVegm-QRSend (ms)	72.0 ± 53.1	67.1 ± 47.4	64.6 ± 53.3	0.89
RVegm-LVegm (ms)	57.9 ± 35.1	62.2 ± 39.5	52.9 ± 29.8	0.47
Q-LVegm (ms)	88.6 ± 45.7	89.2 ± 48.9	87.9 ± 43.3	0.94

BMI: Body mass index; VO_2max: peak oxygen consumption during exercise; QOL: Quality of life score using Minnesota Living with Heart Failure questionnaire; iQRSD: Intrinsic QRS duration; LVp-RVegm: onset of left ventricular pacing to onset of right ventricular intracardiac electrocardiogram; RVegm-LVegm: onset of right ventricular intracardiac electrocardiogram to onset of left ventricular intracardiac electrocardiogram; RVp-LVegm: onset of right ventricular pacing to the onset of left ventricular intracardiac electrocardiogram; LVP-QRSend: onset of left ventricular pacing to the end of QRS complex. Q-LVegm: the interval between the onset of QRS and the onset of left ventricular intra-cardiac electrocardiogram; IVMD: inter-ventricular mechanical delay.

Multivariate correlates of reduction in intrinsic QRS complex duration.

Multivariate analysis of changes in iQRSD performed on pre-defined variables of age, diabetes, gender, IVMD, aetiology and LVEDV showed that only non-ischemic aetiology was a significant correlate of reduction in iQRSD with $\beta = -0.44$, $p = 0.023$ (Table 5).

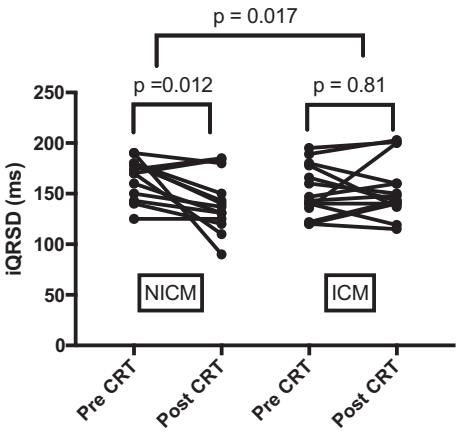
Correlations between reductions in LVp-RVegm and changes in echocardiographic volumes and function

There was no significant correlation between reductions in LVp-RVegm and LVEDV ($r = -0.03$, $p = 0.87$) nor with LVESV ($r = -0.07$, $p = 0.74$) or with changes in LVEF ($r = 0.06$, $p = 0.77$).

Table 2
Effects of cardiac resynchronization therapy on clinical and echocardiographic parameters in the whole cohort.
Normally distributed data are mean ± SD; skewed data are expressed as median values and interquartile values.

Parameters	ALL			NICM			ICM			*p* for heterogeneity
	Pre-CRT	Post-CRT	*p*-Value	Pre-CRT	Post-CRT	*p*-Value	Pre-CRT	Post-CRT	*p*-Value	
Clinical										
VO_2max (ml/min/kg)	13.8 (4.67)	14.1 (5.3)	0.80	15.4 (4.8)	15.9 (5.4)	0.63	12.0 (3.9)	11.8 (4.3)	0.85	
QOL score	40.7 (25.4)	22.9 (22.3)	0.001	35.2 (23.8)	15.4 (12.3)	0.003	46.5 (26.7)	31.0 (27.9)	0.20	0.66
Echocardiographic										
LV EF (%)	31.0 (6.0)	38.0 (10.0)	<0.001	34.5 (5.8)	42.2 (10.2)	0.006	26.9 (3.3)	34.0 (9.0)	0.013	0.87
LVEDV (ml)	193 (69.8)	152 (66.7)	<0.001	145 (121.7–318.7)	109 (37.6)	<0.001	227 (64.8)	197 (60.8)	0.11	0.88
LVESV (ml)	137 (57.5)	98.9 (52.1)	<0.001	106 (45.9)	64.2 (31.5)	<0.001	167.2 (52.4)	133 (45.5)	0.046	0.57
IVMD (ms)	43.6 (44.6)	19.9 (33.9)	0.012	54.6 (42.6)	29.0 (25.0)	0.08	30.8 (45.0)	9.54 (40.9)	0.07	

VO_2max: peak oxygen consumption during exercise; QOL: Minnesota Living with Heart Failure questionnaire; LVEF: left ventricular ejection fraction.
LVED: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; IVMD: interventricular mechanical delay; NICM: non-ischemic cardiomyopathy; ICM: ischemic cardiomyopathy.



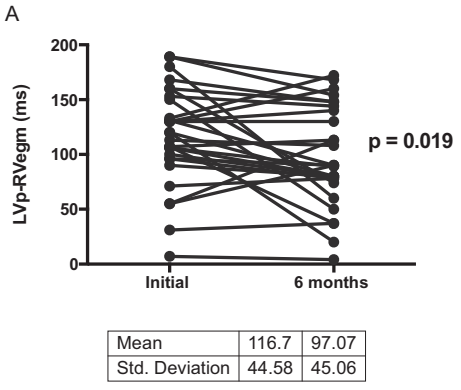
Mean	165.4	140.5	152.6	154.2
Std. Deviation	20.32	28.67	25.62	28.44

Fig. 1. Changes in intrinsic QRS duration in the non-ischemic (NICM) and the ischemic groups.

Discussion

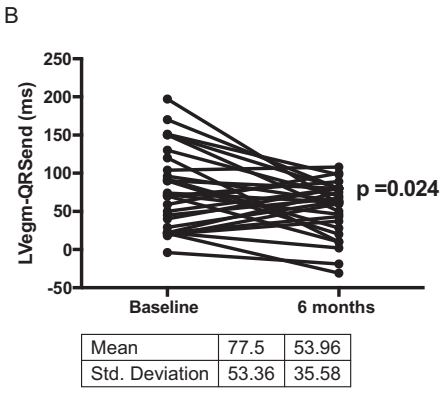
In this study, we were able to demonstrate firstly that our cohort in general had effective cardiac resynchronization at 6 months as shown by significant improvements in echocardiographic and functional parameters. In addition to these, we also observed overall significant improvements in the electrical parameters of iQRSD, LVp-RVegm, and LVegm-QRSend. Importantly, these changes tended to be accentuated in the NICM group rather than the ICM group. Although on univariate analysis, smaller baseline left ventricular volumes were associated with reduction in intrinsic QRS duration, the significance of this finding is not fully clear especially as changes in left ventricular volumes and function were not associated with changes in iQRSD. Similarly, changes in left ventricular volumes and function were not associated with changes in LVp-RVegm. We also found that on univariate analyses, female gender and NICM were significantly associated with subsequent reduction in iQRSD. However, on multivariate analysis, the only significant correlate of extent of reduction in iQRSD was NICM aetiology of heart failure, even when LVEDV was included in the analysis and this is in spite of the significantly greater baseline left ventricular volumes in the NICM group, These findings are consistent with the fact that patients with NICM generally respond better to CRT than patients with ICM aetiology [16,17].

There was no significant difference in mechanical remodelling, as measured by changes in IVMD between ICM and NICM patients. Furthermore, irrespective of the smaller baseline left ventricular volumes in the NICM in our group, both the ICM and the NICM groups achieved significant reduction in LVESV at 6 months and with in-between group reductions being statistically insignificant, ($p = 0.57$ for heterogeneity). Therefore improvement in electrical parameters in the NICM group are independent of changes in mechanical remodelling and left ventricular volumes. There are two potential explanations for the selective reduction in iQRSD and LVp-RVegm in NICM patients: either the absence of extensive myocardial scarring in such patients facilitates



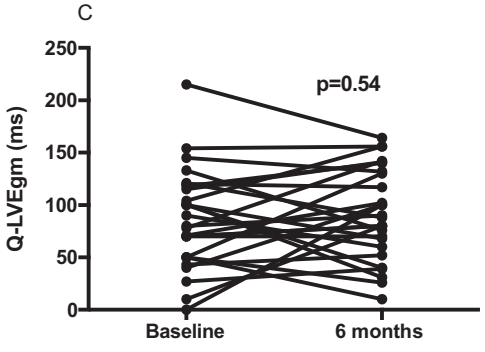
Mean	116.7	97.07
Std. Deviation	44.58	45.06

Paired t-test of left ventricular pacing to the beginning of right ventricular intracardiac electrocardiogram (LVp-RVegm)

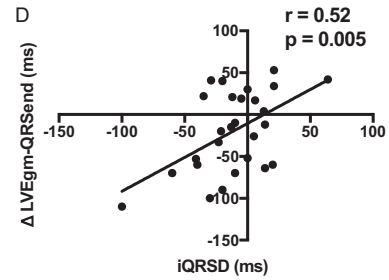


Mean	77.5	53.96
Std. Deviation	53.36	35.58

Paired t- test of onset of left ventricular intra-cardiac electrocardiogram to the end of the surface QRS complex



Mean	86.11	91.48
Std. Deviation	47.13	43.49



Correlation between changes in intrisic QRS duartion and the onset of left ventricular intracardiac electrocardiogram to the end of the surface QRS complex

Fig. 2. Electrical changes 6 months post CRT implant A: LVp-RVegm, paired *t*-test: $p = 0.019$ B: LVegm-QRSend, paired t-test: $p = 0.024$ C: Q-LVegm, paired t-test: $p = 0.54$ D: Correlation between change in intrinsic QRS duration and change in LVegm-QRSend: $r = 0.52$, $p = 0.005$.

Table 3
Electrical changes following cardiac resynchronization therapy.

Parameters	ALL			NICM			ICM			P for heterogeneity
	Baseline	6 months	*p*-Value	Baseline	6 months	*p*-Value	Baseline	6 months	*p*-Value	
iQRSD (ms)	159 (23.6)	148 (29.4)	0.082	165 (20.3)	140 (28.6)	0.012	153 (25.6)	154 (28.4)	0.81	0.017
LVp-RVegm (ms)	117 (44.5)	97.0 (45.0)	0.019	121(31.4)	86.4 (29.0)	0.005	112 (56.2)	109 (56.5)	0.76	0.042
LVEgm-QRSend (ms)	77.5 (53.3)	53.9 (35.5)	0.024	81.5 (60.4)	48.6 (44.3)	0.064	70.6 (51.6)	63.5 (30.9)	0.55	0.21
Q-LVegm (ms)	86.1 (47.1)	91. 4 (43.4)	0.54	90.4 (43.9)	92.3 (46.5)	0.9	82.0 (51.2)	90.6 (42.2)	0.4	
Rvegm-Lvegm (ms)	55.1 (34.4)	57.8 (33.6)	0.48	55.2 (29.5)	52.5 (25.1)	0.87	55.0 (39.5)	63.1 (40.7)	0.25	
RVp-LVegm(ms)	86.9 (39.6)	93.3 (37.9)	0.30	79.2(36.6)	78.6(32.9)	0.93	95.1(42.3)	109 (37.4)	0.17	

Data are normally distributed and are expressed as mean ± SD.
iQRSD: Intrinsic QRS duration; LVp-RVegm: onset of left ventricular pacing to onset of right ventricular intracardiac electrogram; RVegm-LVegm: onset of right ventricular intracardiac electrocardiogram to onset of left ventricular intracardiac electrocardiogram; RVp-LVegm: onset of right ventricular pacing to the onset of left ventricular intracardiac electrocardiogram; LVP-QRSend: onset of left ventricular pacing to the end of QRS complex; NICM: non-ischemic cardiomyopathy; ICM: ischemic cardiomyopathy.

potential changes in electrical conduction, and/or the absence of extensive myocardial scarring is a pre-requisite for CRT-associated improvements in myocardial energetics as postulated by Lidner et al. [18] who found that CRT induces selective increase in regional myocardial oxygen consumption and blood flow in NICM patients but not in ICM which leads to facilitated intra-ventricular electrical conduction. Furthermore, there was no significant correlation between extent of electrical and of mechanical remodelling. Therefore, functional improvement correlates of the extent of electrical remodelling cannot be regarded as surrogates reflecting the beneficial effects of amelioration of mechanical dyssynchrony. It is possible that this better response in the NICM may partly be due to their having significant improvement in electrical remodelling. A sub-analysis of the CARE-HF trial [19] found that QRS duration at 3 months post CRT implant but not QRS duration at baseline, predicted mortality and hospitalized heart failure, again highlighting the benefits associated with improvement in electrical remodelling. Similarly, a retrospective analysis of 337 patients by Iler et al. [20], found after adjustments for confounders that wider QRS duration after CRT implant but not at baseline independently predicted mortality or heart transplantation. Reduction in intrinsic QRS duration in our NICM group may be an indicator that the electrical dyssynchrony in this group reflects functional rather than anatomic block in the left bundle. Consistent with this notion, Auricchio et al. [12] have demonstrated that patients with systolic heart failure and left bundle branch block could have a functional block that potentially could be ameliorated with pacing or an anatomic block that is fixed. Interestingly, two-thirds of their patients with functional block had non-ischemic aetiology of heart failure.

Although, QRS duration and morphology remain the best tools at present to select patients for CRT insertion, recent evidence has cast doubt on the reliability of a simple dichotomization. For instance, Sassone et al. [21] retrospectively evaluated 243 patients and found that in patients with left bundle branch block who underwent CRT insertion, the effect of baseline intrinsic QRS duration on echocardiographic responsiveness and event free survival followed a U-shaped curve with worse outcomes for QRS duration <120–130 ms or >180 ms. Importantly, this analysis includes both ICM and NICM patients. A much greater QRS duration may therefore reflect more extensive and potentially irreversible conduction blocks that not only affect the His-Purkinje system but also the myocardium. Hence we evaluated other measures of electrical remodelling with the subsequent novel finding of significant reduction in conduction times from the left ventricle to the right ventricle with left ventricular-only pacing, which was accentuated in the NICM group only. Given that no significant change occurred in conduction times from the right ventricle to the left ventricle with right ventricular-only pacing, it is likely that the enhanced conduction time with left ventricle-only pacing is due to improvement in left ventricular intramyocardial electrical conduction rather than improvement in the His-bundle conduction. This would agree with previous findings by Auricchio et al. [12] who noted that one-third of their heart failure patients with LBBB had intact transseptal conduction times and near- normal left ventricular endocardial activation times. The authors therefore concluded that in these patients, the LBBB is mainly due to left ventricular intramyocardial conduction delay. A rigorous evaluation of canine models of left bundle branch block by Strik et al. [22] also found that both epicardially and endocardially implanted CRTs improve intramural electrical activation in the left ventricle, again making it less likely that improvement in His-Purkinje conduction post CRT represent the principal basis for improved electrical remodelling.

In our study group, we also found that with pacing briefly turned off at 6 months, CRT significantly reduced the difference between intrinsic QRS duration and the time interval from the onset of QRS complex to the onset of the left ventricular intra-cardiac electrocardiogram, (LVegm-QRSend), which was driven by reduction in intrinsic QRS duration without affecting the time interval between the onset of RV intracardiac electrocardiogram and the onset of LV intra-cardiac electrocardiogram or Q-LVegm. In other words, the time taken to initiate left ventricular depolarization remains unaltered, but once initiated, it takes

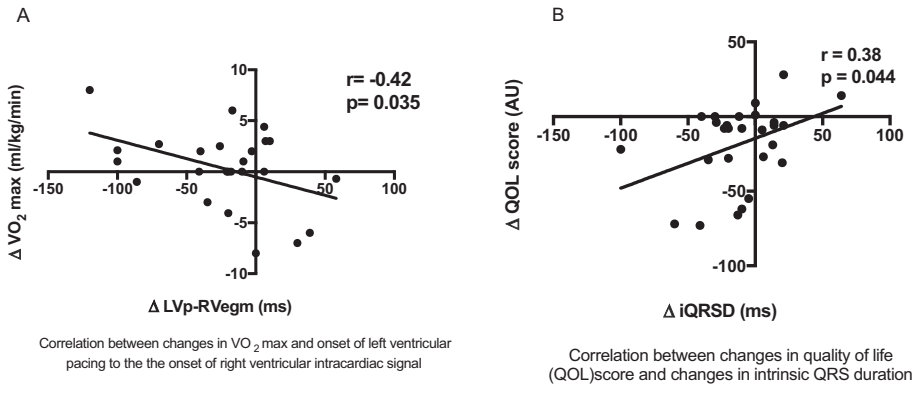


Fig. 3. Correlations between electrical changes and functional status 6 months post CRT implant A: LVp-RVegm and VO_2 max: $r = -0.42$, $p = 0.035$ B: iQRSD and QOL: $r = 0.39$, $p = 0.044$.

Table 4
Univariate determinants of reduction in iQRSD at 6 months post CRT insertion.

Variable	*r*-Value	*p*-Value
Baseline LVEDV (ml)	−0.43	0.037
Baseline LVESV (ml)	−0.40	0.049
Baseline LVEF (%)	0.20	0.32
Baseline IVMD (ms)	−0.02	0.89
Change in LVEDV (ml)	0.21	0.31
Change in LVESV (ml)	0.18	0.39
Change in LVEF (%)	0.14	0.51
Age	0.03	0.87
Aetiology	0.42	0.028
Diabetes	0.03	0.89
Gender	0.41	0.031

LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction, IVMD: Inter-ventricular mechanical delay.

less time to complete ventricular contraction. This finding also supports the hypothesis of improvement in left ventricular intra-mural conductivity rather than His-bundle conduction or right ventricular conduction. This could also explain why there was no improvement in the RVegm-LVegm which measures time interval for spontaneous depolarization of both ventricles. When all these measurements of electrical remodelling are considered together, we can conclude that in our cohort, CRT did not result in improvement in RV and/or His-bundle conduction but in improvement in left ventricular intra-myocardial conduction. Interestingly, Knuuti et al. [23] in their study of ten patients with NICM found that CRT improved regional left ventricular myocardial oxidative but had no effect on the right ventricular myocardial oxidative metabolism at rest.

The consistent finding of improvement in electrical parameters in the NICM group in our study may contribute to the selective reduction in all-cause mortality of CRT-D over CRT-P only in patients with ischemic aetiology of heart failure but not in patients with NICM [24], perhaps indicating that CRT-P resulted in improvements in electrical remodelling in the NICM group only and thus mitigating the need for high voltage therapy.

Interestingly, the improvement in LVp-RVegm in our NICM group was also significantly correlated directly with change in VO_2 max at 6 months although no overall change occurred in VO_2 max itself. No study, to the best of our knowledge has shown this relationship, although improved ventricular activation has been shown to result in improved haemodynamics [22]. Further re-enforcing the postulate that improvement in electrical remodelling could lead to improvement in functional status is our finding of a direct correlation between improvement in QOL score and reduction in intrinsic QRS duration at 6 months, in spite of the fact that in our cohort, change in QOL did not correlate with changes in measures of mechanical dyssynchrony. Our findings would therefore suggest that CRT-induced reversal of electrical remodelling could potentially lead to improvement in functional status independent of improvement in mechanical effects. The mechanisms underlying this observation remain uncertain, but a previous study found that reduction in intrinsic QRS duration 12 months post CRT implant was associated with improvement in NYHA functional status [25].

Table 5
Multivariate determinants of reduction in iQRSD at 6 months following CRT.

Parameter	Standardized coefficients beta	*p*-Value
Diabetes	0.23	0.24
Gender	0.27	0.18
Age	−0.30	0.76
IVMD (ms)	−0.03	0.85
Aetiology	−0.44	0.023
LVEDV (ml)	−0.18	0.38

IVMD: interventricular mechanical delay; LVEDV: left ventricular end-diastolic volume.

Limitations

Our study is limited by the small number of participants with the resultant potential for 'false negative' results by virtue of Type II error.

The NICM group also had higher left ventricular systolic functions at baseline, which might contribute, to some of the observed findings. However both groups responded well echocardiographically and clinically. In addition both groups had similar baseline electrical parameters thus suggesting a disconnect between 'severity' of mechanical and electrical remodelling.

Conclusion

CRT reverses electrical remodelling and selectively improves left ventricular intramyocardial electrical conduction in patients with non-ischemic aetiology of heart failure. There seems to be a substantial disconnect between 'severity' of mechanical and electrical changes. Ultimately, improvements in electrical remodelling are associated with improvement in functional status independent of changes in echocardiographic mechanical dyssynchrony.

Disclosure of conflict of interest

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