Improvement in left ventricular intrinsic dyssynchrony with cardiac resynchronization therapy

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Abstract

Objective: Cardiac resynchronization therapy (CRT) has been shown to induce a structural and electrical remodeling; the data on whether left ventricle (LV) reverse remodeling is associated with restitution of intrinsic contraction pattern are unknown. In this study, we investigated the presence of improvement in left ventricular intrinsic dyssynchrony in patients with CRT.

Methods: A total of 45 CRT recipients were prospectively studied. Dyssynchrony indexes including interventricular mechanical delay (IVMD) and tissue Doppler velocity opposing-wall delay (OWD) as well as QRS duration on 12-lead surface electrocardiogram were recorded before CRT device implantation. After 1 year, patients with chronic biventricular pacing were reprogramed to VVI 40 to allow the resumption of native conduction and contraction pattern. After 4–6 h of intrinsic rhythm, QRS duration and all echocardiographic measurements were recorded. Dyssynchrony was defined as IVMD >40 ms and OWD >65 ms. CRT response was defined by a ≥15% reduction in left ventricular end-systolic volume (LVESV) at a 12-month follow-up.

Results: Thirty-two patients (71%) showed response to CRT. The native QRS duration reduced significantly from 150±12 ms to 138±14 ms ($p<0.001$), and dyssynchrony indexes showed a significant improvement only in responders. The mean OWD reduced from 86±37 ms to 50±29 ms ($p<0.001$), and the mean IVMD decreased from 55±22 ms to 28±22 ms ($p<0.001$) in responders. The reduction in LVESV was significantly correlated with ΔOWD ($r=0.47$, $p=0.001$), ΔIVMD ($r=0.45$, $p=0.001$), and ΔQRS ($r=0.34$, $p=0.022$).

Conclusion: Chronic CRT significantly improves LV native contraction pattern and causes reverse remodeling in dyssynchrony.

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Keywords: CRT, intrensek dissenkroni, native QRS duration, reverse remodeling

Introduction

Cardiac resynchronization therapy (CRT) is effective for patients with symptomatic heart failure, widened QRS, and reduced ejection fraction (EF) (1–3). CRT is associated with electrical and mechanical reverse remodeling. Although it has been shown to induce a structural and electrical remodeling (ER), little is known whether left ventricle (LV) reverse remodeling is associated with restitution of intrinsic contraction pattern.

The beneficial effects of CRT have been attributed to the restoration of synchrony within the LV (4–7). Some investigators have reported that a change in LV dyssynchrony immediately after CRT is a marker of the mid-term or long-term response to CRT (4, 8). Whether these improvements are due to the short-term effects of improvement in synchrony or contractile performance or due to long-term improvement in ventricular structure and function remains insufficiently elucidated.

We sought to determine 1) whether chronic CRT induces an improvement in intrinsic dyssynchrony and 2) if changes in the intrinsic dyssynchrony and native conduction pattern correlate with response to CRT.

Methods

We prospectively studied a series of 45 heart failure patients who underwent CRT device implantation. The protocol was ap-

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proved by the Local Ethics Committee, and a written informed consent was obtained from all the patients. All the patients had New York Heart Association functional class III or IV heart failure despite receiving optimal pharmacological therapy and had left bundle branch block (LBBB) morphology and LVEF <35%. Patients who were pacemaker dependent or who were in atrial fibrillation were excluded.

A biventricular pacing system was implanted with a standard right ventricular (RV) apical lead and LV lead positioned through the coronary sinus in an epicardial vein targeting posterolateral or lateral branches. After implantation, patients underwent a standardized echocardiography-based atrioventricular (AV) and ventriculoventricular (VV) optimization in order to increase the rate of biventricular pacing.

All the patients underwent transthoracic echocardiography before device implantation. Patients were imaged in the left lateral decubitus position using a commercially available system (VIVID 7, General Electric-Vingmed Ultrasound, Horten, Norway). Images were obtained using a 2.5-MHz broadband transducer at a depth of 16 cm in the parasternal and apical views (standard long-axis, 2- and 4-chamber images). Routine two-dimensional and tissue Doppler imaging (TDI) cine loops were obtained. LVEF was calculated from the conventional apical 2- and 4-chamber images using the biplane Simpson's technique (9).

Dyssynchrony indexes included in this study were interventricular mechanical delay (IVMD) and opposing-wall delay (OWD). IVMD was calculated from routine pulsed Doppler as previously described (10). IVMD was determined as the difference between the RV and LV pre-ejection time, with >40 ms predefined as significant dyssynchrony (11). Longitudinal dyssynchrony was OWD, defined as the maximal difference in peak velocity at basal and mid segments in opposing walls for each view. Significant longitudinal dyssynchrony by TDI was predefined as the maximal OWD in one view >65 ms (10, 12).

12-lead surface electrocardiogram (ECG) tracings were recorded on a chart paper at a speed of 25 mm/s with a gain setting of 10 mm/mV. QRS duration was defined as the widest interval in any of the 12 leads. QRS duration was manually measured and double checked with the computer output.

At 12 months of follow-up, CRT devices were reprogramed to VVI mode at 40 bpm to assess the intrinsic QRS duration and intrinsic dyssynchrony. After 4–6 hours of native rhythm, a surface ECG was recorded and all echocardiographic parameters were obtained again.

Echocardiographic response to CRT was defined by a ≥15% reduction in left ventricular end-systolic volume (LVESV) at a 12-month follow-up (13).

Statistical analysis

All analyses were performed using the statistical software program SPSS version 13.0 (IBM, Armonk, NY). Continuous variables were expressed as mean±standard deviation, median (25^{th}–75^{th} percentiles), and categorical variables were expressed as counts (percentages). Categorical variables were compared using the Yates' χ^2 test and Monte-Carlo χ^2 test. The Mann–Whitney U test was used to assess differences in clinical and baseline echocardiographic findings between the responders and non-responders. A comparison of the echocardiographic variables before and after CRT was performed using paired sample t-test, Wilcoxon signed rank test, or McNemar χ^2 test. Spearman correlation coefficients were used to evaluate the parameters associated with the changes in LVESV. A value of p <0.05 was considered statistically significant.

Table 1. Comparison of baseline and 1st year of clinical and echocardiographic measurements [mean±SD/median (25^{th}–75^{th} percentiles)]

	Baseline	1 year	*P*
LVEDD, mm	67.1 (60.3–74.3)	68.0 (56.5–70.7)	0.003[a]
LVESD, mm	54.0 (49.0–62.6)	52.0 (43.0–55.0)	<0.001[a]
LAD, mm	45.0 (40.0–47.0)	43.0 (40.0–48.0)	0.006[a]
LVEF, %	19.9 (15.0–28.5)	35.0 (32.0–44.0)	<0.001[a]
LVEDV, mm^3	267.0 (219.1–304.2)	163.0 (103.0–211.1)	0.015[a]
LVESV, mm^3	207.1 (156.5–238.5)	230.0 (198.1–314.8)	<0.001[a]
QRS, ms	150.0 (140.0–160.0)	140.0 (130.0–153.0)	<0.001[a]
TDI dyssynchrony by OWD ≥65 ms, n (%)	33 (73)	15 (33)	<0.001[b]
Mean OWD, ms	95±51	64±44	<0.001[c]
IVMD ≥40 ms, n (%)	31 (69)	18 (40)	0.002[b]
Mean IVMD, ms	54±24	32±23	<0.001[c]

IVMD - interventricular mechanical delay; LAD - left atrial diameter; LVEDD - left ventricular end-diastolic diameter; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESD - left ventricular end-systolic diameter; LVESV - left ventricular end-systolic volume; OWD - opposing wall delay. [a]: compare with Wilcoxon t Test; [b]: compare with McNemar chi-square Test; [c]: compared with paired samples t-test

Results

A total of 45 patients (23 males; mean age, 64±14 years) were included in the study. Thirty-five patients had non-ischemic etiology. All the patients had a biventricular implantable cardioverter defibrillator (InSync ICD, Medtronic Inc, Minneapolis, Minnesota).

After 1 year, left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD), end-diastolic volume (LVEDV), LVESV, and left atrial diameter significantly decreased and LVEF increased (Table 1). The prevalence of TDI dyssynchrony by OWD >65 ms was 73% (n=33) in the whole study group. IVMD >40 ms was observed in 69% (n=31) of the patients. The mean OWD was 95±51 ms and the mean IVMD was 54±24 ms before CRT device implantation. Significant dyssynchrony was observed less often at 12 months compared with baseline for both OWD >65 ms and IVMD >40 ms. The mean OWD was 64±44 ms and mean IVMD was 32±23 ms after CRT device implantation (p<0.001). The native QRS duration prior to CRT was 150.0 ms (140.0–160.0) and was shortened to 140.0 ms (130.0–153.0) (p<0.001).

Table 2. Baseline clinical and echocardiographic parameters of responders and non-responders

	Responders (n=32)	Non-responders (n=13)	*P*
Age, years	64±15	62±13	0.450[a]
Male, (%)	16 (50)	7 (54)	0.810[b]
Non-ischemic CMP, (%)	24 (75)	11 (85)	0.490[b]
LVEDD, mm	67.0 (60.2–72.8)	72.0 (60.3–75.0)	0.350[a]
LVESD, mm	54.0 (49.3–60.5)	60.3 (40.8–63.9)	0.840[a]
LAD, mm	45.0 (40.0–46.0)	45.0 (41.0–50.0)	0.300[a]
LVEF, %	20.0 (15.0–29.0)	19.6 (17.2–23.9)	0.740[a]
LVEDV, mm^3	256.6 (197.5–301.5)	288.2 (283.0–346.6)	0.350[a]
LVESV, mm^3	200.0 (156.0–235.5)	215.9 (192.3–272.3)	0.230[a]
QRS, ms	160.0 (140.0–160.0)	150.0 (135.5–160.0)	0.480[a]
TDI dyssynchrony by OWD ≥65 ms, n (%)	22 (69)	11 (85)	0.240[b]
Mean OWD, ms	86±37	119±74	0.150[a]
IVMD ≥40 ms, n (%)	22 (69)	9 (69)	0.680[b]
Mean IVMD, ms	55±22	52±29	0.980[a]
LV lead position			
Posterolateral vein	18	7	1.000[b]
Posterior vein	6	3	
Lateral vein	8	3	

CMP - cardiomyopathy; IVMD - interventricular mechanical delay; LAD - left atrial diameter; LVEDD - left ventricular end-diastolic diameter; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESD - left ventricular end-systolic diameter; LVESV - left ventricular end-systolic volume; OWD - opposing wall delay. [a]: compare with Mann-Whitney U test; [b]: compare with Monte Carlo and Yates' chi- square test

Thirty-two patients (71%) showed response to CRT. The baseline clinical and echocardiographic findings of responders and non-responders showed no statistically significant differences (Table 2). There were no significant differences in the LV lead positions between responders and non-responders. In both groups, the majority of the LV leads were positioned in the posterolateral veins (Table 2). Although the prevalence of TDI dyssynchrony by OWD >65 ms tended to be higher in non-responders, the difference was not statistically significant.

The QRS width reduced significantly from 160 ms (140–160 ms) to 130 ms (130–150 ms) ($p<0.001$), and dyssynchrony indexes showed a significant improvement only in responders. The prevalence of intraventricular dyssynchrony reduced from 69% to 19% ($p<0.001$). Similarly, the number of patients with interventricular dyssynchrony decreased from 69% to 31% ($p=0.01$). Comparison of baseline and 12 months of clinical and echocardiographic data in responders and non-responders are represented in Table 3.

The reduction in LVESV was significantly correlated with ΔOWD ($r=0.47$, $p=0.001$), ΔIVMD ($r=0.45$, $p=0.001$) and ΔQRS ($r=0.34$, $p=0.022$).

Discussion

To the best of our knowledge, our study is the first to show a significant improvement in LV intrinsic dyssynchrony after 1 year of permanent CRT. The current studies regarding CRT have investigated mechanical remodeling while CRT is active. Most of these studies have demonstrated a significant improvement in the left ventricular hemodynamics and mechanics (14-16). The current study adds value to the CRT field by demonstrating reverse remodeling in intrinsic dyssynchrony.

The major pathophysiological entity that is treated using CRT is an abnormality of LV regional mechanical activation (17). Previous studies have reported the importance of mechanical remodeling after CRT, but they have focused on effects during biventricular pacing as opposed to effects on the native contraction pattern. Bleeker et al. (4) assessed dyssynchrony using color-coded TDI in 100 patients scheduled for CRT device implantation. At the 6-month follow-up, significant improvement in LV function was observed in 85% of patients who were classified as responders. Immediately after pacing, the responders demonstrated a significant reduction in LV dyssynchrony from 115±37 to 32±23 ms. However, no significant reduction was observed in non-responders. In our study, 71% of patients showed response to CRT, and native dyssynchrony indexes, along with intrinsic QRS duration, showed a significant improvement only in responders.

CRT not only induces structural reversal but also restores electrical dyssynchrony in the failing heart. The deterioration of intraventricular conduction by inducing iatrogenic LBBB further affects LV systolic dysfunction and can be reversed using biventricular pacing (18). There is a relationship between electrical dispersion that causes QRS widening and dyssynchrony. QRS narrowing after the onset of biventricular pacing is a sign of electrical resynchronization and is frequently associated with therapeutic response CRT. Although paced QRS duration has been explored comprehensively, little is known about changes in native QRS duration induced by CRT. Till now, only rare studies have assessed whether alteration in native QRS duration might be correlated with favorable structural changes and CRT response. Sebag et al. (19) observed a significant intrinsic QRS narrowing, although QRS complex did not normalize after 1 year of permanent pacing. The electrocardiographic response defined as a reduction of at least 20 ms was found to be associated with a better clinical and echocardiographic response. Yang et al. (20) showed that native QRS narrowing was associated with beneficial response and greater improvements in echocardiography. Similarly, Karaca et al. (21) showed that reversed ER, by means of narrowing of the intrinsic electrocardiographic QRS duration after CRT, has clinical and prognostic implications. A narrowed intrinsic QRS interval compared with that at baseline was found to be associated with improved functional status and higher CRT response. Consistently with the recent studies, our study once

Table 3. Comparison of baseline and 12 months of clinical and echocardiographic measurements in responders and non-responders [mean±SD/ median (25th–75th percentiles)]

	Responder			Non-responder		
	Baseline	1 year	*P*	Baseline	1 year	*P*
LVEDD, mm	67.0 (60.2–72.8)	66.7 (56.0–69.0)	0.002[a]	72.0 (60.3–75.0)	70.7 (57.0–74.8)	0.505[a]
LVESD, mm	54.0 (49.3–60.5)	52.0 (43.8–55.0)	<0.001[a]	60.3 (40.8–63.9)	53.9 (39.0–63.5)	0.063[a]
LAD, mm	45.0 (40.0–46.0)	39.0 (34.0–49.3)	0.133[a]	45.0 (41.0–50.0)	45.0 (42.0–52.0)	0.630[a]
LVEF, %	20.0 (15.0–29.0)	39 (34.0–49.3)	<0.001[a]	19.6 (17.2–23.9)	33.6 (26.7–34.0)	0.001[a]
LVEDV, mm^3	256.6 (197.5–301.5)	224.9 (165.0–246.0)	0.005[a]	288.2 (283.0–346.6)	314.8 (254.0–339.6)	0.916[a]
LVESV, mm^3	200.0 (156.0–235.5)	112.0 (98.0–164.1)	<0.001[a]	215.9 (192.3–272.3)	211.1 (177.0–247.2)	0.001[a]
QRS, ms	160.0 (140.0–160.0)	130.0 (130.0–150.0)	<0.001[a]	150.0 (135.5–160.0)	140.0 (130.0–160.0)	0.167[a]
OWD ≥65 ms, n (%)	22 (69)	6 (19)	<0.001[b]	11 (85)	9 (69)	0.170[b]
Mean OWD, ms	86±37	50±29	<0.001[c]	119±74	99±55	0.090[c]
IVMD ≥40 ms, n (%)	22 (69)	10 (31)	0.001[b]	9 (69)	8 (62)	0.580[b]
Mean IVMD, ms	55±22	28±22	<0.001[c]	52±29	43±23	0.090[c]

IVMD - interventricular mechanical delay; LAD - left atrial diameter; LVEDD - left ventricular end-diastolic diameter; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESD - left ventricular end-systolic diameter; LVESV - left ventricular end-systolic volume; OWD - opposing wall delay. [a]:compare with Wilcoxon t-test; [b]: compare with McNemar chi -square test; [c]: compare with paired samples t-test

again confirmed that the narrowing of native QRS duration is associated with increased echocardiographic response after CRT. ER of native conduction could reflect electrical reversal imposed by CRT, and it could be used to screen non-responders during follow-up period.

Despite ΔLVESV being significantly correlated with ΔQRS, we could not find any relation between the decrease in QRS duration and the improvement in dyssynchrony indices. Furthermore, Stockburger et al. (22) did not find any association between structural and ER. Despite LVEDD reduction with CRT, electrical activation did not recover in their LBBB patients. These results suggest that some factors other than the shortening of QRS duration may also influence the reverse mechanical remodeling. Alternative mechanisms such as cellular and molecular effects of CRT are still being investigated. A study by Kirk et al. (23) has enhanced our understanding of the complex pathophysiology that underlies dyssynchronous heart failure. Dyssynchrony induces regional difference in protein expression and has important consequences at the global and cellular level. In a canine model of ventricular dyssynchrony, Spragg et al. (24) demonstrated significant transmural and trans-chamber gradients of stress-response kinases, calcium handling, and gap junction proteins. Improving synchrony of contraction using CRT reverses maladaptive growth remodeling, increases cell-survival signaling, enhances Ca^{2+} handling, and boosts β-adrenergic responsiveness among other effects (23, 25, 26). Simply restoring electrical synchrony using CRT not only improves heart function and energetics but also has a beneficial effect on the molecular and cellular biology. The effects of cellular and molecular changes induced by CRT on reverse mechanical remodeling need to be fully defined.

Study limitations

We acknowledge that there were limitations in this study. The major weakness of our study was the small sample size and the lack of clinical outcome variables such as death/hospitalization/NYHA status. Also, did not investigate the intra- and interventricular dyssynchrony using more sophisticated dyssynchrony indexes. However, TDI dyssynchrony by OWD >65 and IVMD >40 ms are the most commonly used markers of intraventricular and interventricular dyssynchrony in real-life clinical practice.

Conclusion

Chronic CRT significantly improves LV native contraction pattern and causes reverse remodeling in dyssynchrony. Further studies are needed to assess the mechanism of improvement in intrinsic contraction pattern.

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