Clinical Investigation

Native Electrocardiographic QRS Duration after Cardiac Resynchronization Therapy: The Impact on Clinical Outcomes and Prognosis

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ABSTRACT

Background: We investigated whether reversed electrical remodeling (RER), defined as narrowing of the native electrocardiographic QRS duration after cardiac resynchronization therapy (CRT), might predict prognosis and improvement in echocardiographic outcomes.

Methods and Results: A total of 110 CRT recipients were retrospectively analyzed for the end points of death and hospitalization during 18 ± 3 months. Native QRS durations were recorded at baseline and 6 months after CRT (when pacing was switched off to obtain an electrocardiogram) to determine RER. CRT response and mitral regurgitation (MR) improvement were defined as ≥15% reduction in left ventricular end-systolic volume and absolute reduction in regurgitant volume (RegV) at 6 months, respectively. Overall, 48 patients (44%) had RER, which was associated with functional improvement (77% vs 34%; $P < .001$) and CRT response (81% vs 52%; $P < .001$) compared with those without RER. The change in the intrinsic QRS duration correlated with the reduction in RegV ($r = 0.51$; $P < .001$) and in tenting area ($r = 0.34$; $P < .001$). RER was a predictor of MR improvement ($P = .023$), survival ($P = .043$), and event-free survival ($P = .028$) according to multivariate analyses.

Conclusions: Narrowing of the intrinsic QRS duration is associated with functional and echocardiographic CRT response, reduction in MR, and favorable prognosis after CRT. (*J Cardiac Fail 2016;22:772–780*)

Key Words: Native QRS duration, reversed electrical remodeling, cardiac resynchronization therapy response, mitral regurgitation, prognosis.

Cardiac resynchronization therapy (CRT) is an established therapeutic option for systolic heart failure concomitant with electrical dyssynchrony.[1–4] The extent of baseline electrical dyssynchrony is currently determined by prolongation of the QRS duration with a left bundle branch block (LBBB) morphology, which is a well known predictor of CRT response.[3,4] Restoration of the dyssynchronous conduction within the His-Purkinje system by means of biventricular pacing has been proposed as the mechanism of action that correlates with the clinical and echocardiographic improvements after CRT.[4,5] Narrowing of the native QRS duration as a marker of reversed electrical remodeling (RER) after CRT has been shown in previous studies to correlate with favorable structural changes and CRT response.[5,6]

Mitral regurgitation (MR), a significant prognostic marker in patients with heart failure, has been shown to be reduced by CRT, although the precise mechanisms are not fully understood.[7–9] The impact of native QRS narrowing on the degree of MR and on the geometric changes of the mitral valve following CRT have not been addressed previously. The objectives of the present study were: 1) to evaluate the relationship of CRT-induced RER to the improvement in functional status, CRT response, MR, and mitral geometry; and 2) to test the hypothesis that narrowing of the native QRS

duration might predict prognostic outcomes such as reduction in MR severity and decrease in death and hospitalization during follow-up.

Methods

Patient Selection and Study Design

A total of 172 patients receiving a biventricular device with or without a defibrillator (CRT-D or CRT-P) were retrospectively analyzed in the study. Compatibly with current guidelines,[10] all patients had a left ventricular ejection fraction (LVEF) ≤35%, an increased QRS duration (≥120 ms), and symptomatic heart failure (New York Heart Association [NYHA] functional class II–IV) despite optimal medical therapy. Patients with right ventricular pacing upgraded to CRT and those with pacemaker dependency were excluded. Patients with organic MR, defined as moderate to severe annular calcifications, rheumatic valve disease, mitral valve prolapse with or without flail leaflet/chordae, or a history of mitral valve repair or replacement, were excluded.[11] Patients with inadequate image quality to calculate left ventricular (LV) volumes (n = 12) and those with trivial MR that precluded the quantification of MR (n = 44) were also excluded from the analyses. Patients who failed to continue follow-up visits (n = 6) were excluded, leading to a final study population of 110 CRT recipients with MR. The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from every participant.

Electrocardiographic Recordings

Baseline, post-implantation (paced), and follow-up intrinsic (when the CRT device was switched off) 12-lead electrocardiographic (ECG) tracings were recorded on a chart paper at a speed of 50 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. Baseline QRS morphologies were recorded as either LBBB or non-LBBB based on well defined criteria.[12] Paced QRS intervals were calculated after echocardiographic device optimization, which was performed during the hospital stay. At 6 months of follow-up, CRT devices were switched off for 10 seconds to assess the native conduction. The intrinsic QRS duration on the follow-up ECG was included in the study data to determine RER, which was defined as narrowing of the native QRS duration after CRT.

Device Implantation and Programming

Transvenous approach via the left subclavian vein was used to implant CRT-D or CRT-P devices under local anesthesia in the vast majority of patients. The right atrial lead was located in the right atrial free wall (in patients with sinus rhythm) and the right ventricular lead was located in the right ventricular apex or the outflow tract according to the operator's choice. Following coronary sinus angiography, the LV lead was inserted preferably in the posterolateral vein as recommended.[13] In case of anatomic difficulties in implanting the LV lead in the optimal position (in 12 patients), minimal invasive surgical approach was preferred to implant an epicardial LV lead. Use of a defibrillator lead depended on the clinical indication or the operator's choice. Initial device programming was performed by setting default values of 100 ms for the sensed AV interval, 130 ms for the paced AV interval, and 20 ms for the VV interval (LV preceding RV). Both AV and VV intervals were checked before patient discharge and optimized with a previously described echocardiographic method in case of necessity.[14] The ECG obtained after optimization was used to measure the paced QRS duration to include in the study data.

Echocardiographic Analyses

Baseline and 6-month follow-up echocardiography were performed with the use of a commercially available system (Vivid E9; General Electric, Milwaukee, Wisconsin) using a 3.5-MHz transducer. The cine-loops for measurements of LV volumes, mitral deformation indices, and MR quantification were recorded in the left lateral decubitus position. Offline analysis was performed by 2 expert sonographers who were blinded to the study data.

LV Measures

Apical 2- and 4-chamber views were used to calculate LV volumes in both end-systole (LVESV) and end-diastole (LVEDV); once obtained, the results were used to calculate the left ventricular ejection fraction (LVEF) by means of the biplane Simpson method.[15]

Mitral Valve Deformation and Quantification of MR

Mitral geometry was assessed in the parasternal long-axis view at mid-systole. Tenting area (TA) was measured as the area enclosed between the annular plane and the coaptation point of the mitral leaflets.[16] Tenting distance (TD) was measured as the perpendicular line between the annular plane and the coaptation point of the mitral valve leaflets.[16] The change in TA at 6 months compared with baseline was defined as ΔTA.

The proximal isovelocity surface area (PISA) method was used to determine the severity of MR, as described previously.[17] MR was quantified as the effective regurgitant orifice area (EROA) and the regurgitant volume (RegV). Depending on the change in RegV at 6 months, patients were defined as either MR responders (RegV reduced at follow-up) or MR nonresponders (no change or an increase in RegV) at 6 months. The change in RegV at 6 months compared with baseline was defined as ΔRegV.

Reproducibility

Twenty randomly selected patients were retrospectively reevaluated to test the reproducibility of the main

echocardiographic parameters in the study. Intraobserver variability was found to be 8% and interobserver variability as 9% for measuring RegV, and these values were found to be 5% and 8%, respectively, for measuring LVESV, all of which were within a clinically acceptable range.

Follow-Up and Definition of Outcomes

The end points of the study were designated as all-cause death and heart failure–related hospitalization. Patients were followed for a mean period of 18 ± 3 months (range 1–24 mo) beginning from the day of CRT implantation. Regular clinical visits were scheduled for intervals of 3 months. The follow-up data were obtained through regular visits, by telephone calls, and from hospital records. Only 1 event was counted for each patient during the follow-up.

Improvement in functional status was defined as ≥ 1 grade decrease in NYHA functional class at 6 months of follow-up. Response to CRT was defined as a $\geq 15\%$ reduction in LVESV at 6 months. Improvement in MR (MR response) was defined as absolute reduction in RegV at 6 months compared with baseline. The study population (n = 110) was divided into 2 groups based on narrowing of the intrinsic QRS interval (RER) assessed at 6 months: patients without RER (n = 62) and patients with RER (n = 48). Both groups were compared regarding the baseline clinical, ECG, and echocardiographic features, as well as the outcome variables defined as functional improvement, CRT response, MR response, death, and hospitalization.

Statistical Analyses

Statistical analyses were conducted with the use of SPSS (version 17.0; SPSS, Chicago, Illinois). Data were expressed as mean $\pm$ SD for continuous variables and percentage for categoric variables. Shapiro-Wilk test was used to test for normal distribution. Continuous variables were compared with the use of Student t test for independent samples that showed normal distribution, and the Mann-Whitney U test was used for nonnormally distributed samples based on RER. Associations of the categoric variables between groups were tested with the use of chi-square test. Comparison of the baseline and the follow-up values for NYHA functional class, intrinsic QRS duration, and several echocardiographic parameters according to the status of RER was performed by means of paired-sample t test and the results were presented in a table. Statistical significance was defined as a P value <.05 for all comparisons. Pearson correlation analysis was used to test the relationship between (1) the change in intrinsic QRS duration and the change in RegV at 6 months and (2) the change in intrinsic QRS duration and the change in TA. The results of the correlations were shown on separate scatter-dot graphs with the corresponding r and P values.

Cox proportional hazard models were separately created to determine the predictors of all-cause death and combined death/hospitalization after CRT. In univariate analysis, variables showing significant differences with outcome ($P < .05$)

were included in the multivariate analysis. Baseline QRS duration, LBBB morphology, paced QRS duration, follow-up intrinsic QRS duration, and RER (positive ΔQRS) were the independent variables to predict outcome. Time variables were defined as time to death and time to death or hospitalization in months. The results of the Cox regression were reported as hazard ratios (HRs), 95% confidence intervals (CIs), and P values in a table.

Univariate and multivariate logistic regression analyses were performed to define the independent predictors of MR improvement after CRT. Statistically significant ($P < .05$) variables in the univariate analysis were tested in the multivariate model. Baseline QRS duration, paced QRS duration, follow-up intrinsic QRS duration, RER, baseline LVEF, baseline LVESV, and TA were the independent variables, whereas the MR response was the dependent variable of the model. Results of the regression analyses were expressed as the P value and odds ratio (OR) with 95% CI and presented in a table.

Kaplan-Meier curves were generated to analyze the effect of RER on survival and event-free survival during the time course of the study. Each analysis was demonstrated with a separate graphic, and the results were expressed as log rank and P values.

Results

The study population had a mean age of 64 ± 11 years (36% female), mean LVEF of $26.5 \pm 5.7\%$,and mean baseline QRS duration of 160.5 ± 20.9 ms. Overall, 48 patients (44%) had RER, defined as narrowing of the intrinsic QRS duration assessed while CRT was switched off at 6 months. Comparison of the baseline features of the study population based on RER is presented in Table 1. In general, the 2 groups were similar except for the etiology of heart failure and the paced QRS durations after CRT. Patients with RER were more likely to have nonischemic cardiomyopathy (60% vs 55%; $P = .032$) and had shorter paced QRS durations (149.3 ± 20.1 ms vs 160.6 ± 26.5 ms; $P = .012$) than patients without RER.

Overall, the end point of all-cause death was reached in 17 patients (4 patients with RER vs 13 patients without RER), and combined death/hospitalization was observed in 43 patients (12 patients with RER vs 31 patients without RER) during the mean follow-up of 18 ± 3 months (range 1–24 mo). A total of 71 patients (65%) responded to CRT, and MR improvement was observed in 58 patients (53%) at 6 months.

Table 2 presents the baseline and CRT-induced changes in echocardiographic parameters (including LVESV, LVEDV, LVEF, EROA, RegV, TA, and TD), as well as the change in severe functional status (NYHA III/IV) and intrinsic QRS duration in the overall population and in groups based on RER. Reduction in NYHA III/IV status and improvements in LV volumes/function were observed in the overall population and in both RER groups. However, parameters of MR quantification (EROA and RegV) and mitral geometry (TA and TD) seemed to improve only in patients with RER and to worsen in patients without RER (all P values <.05). The overall population had a minor reduction

Table 1. Comparison of the Baseline Demographic, Clinical, and Electrocardiographic Features of the Study Population According to the Narrowing of the Intrinsic QRS Duration Following CRT, Represented as Reversed Electrical Remodeling (RER) − or RER+

	Overall (n = 110)	RER− (n = 62)	RER+ (n = 48)	P Value
Age, y*	66 (61–75)	64 (58–71)	67 (62–73)	.096
Female sex, % (n)	36% (40)	35% (22)	38% (18)	.829
BSA, m²*	1.86 (1.73–1.99)	1.89 (1.73–1.99)	1.83 (1.72–2.02)	.795
BMI, kg/m²	27.5 ± 4.7	27.3 ± 4.6	27.7 ± 5.0	.699
Nonischemic etiology, % (n)	57% (63)	55% (34)	60% (29)	.032
Hypertension % (n)	73% (80)	68% (42)	75% (36)	.124
Diabetes, % (n)	33% (36)	37% (23)	27% (13)	.271
Hyperlipidemia, % (n)	46% (51)	51% (32)	39% (19)	.074
Atrial fibrillation,† % (n)	27% (30)	29% (18)	25% (12)	.641
NYHA III/IV, % (n)	64% (71)	60% (37)	71% (34)	.229
CRT-D, % (n)	89% (98)	87% (54)	92% (44)	.162
LBBB morphology	85% (94)	83% (51)	89% (43)	.120
Baseline QRS duration, ms	160.5 ± 20.9	158.8 ± 21.8	162.7 ± 19.6	.326
QRS ≥150 ms, % (n)	65% (71)	60% (37)	71% (34)	.225
Paced QRS duration (ms)	155.9 ± 25.0	160.6 ± 26.5	149.3 ± 20.1	.012
Hb, g/dL	12.4 ± 1.6	12.3 ± 1.8	12.7 ± 1.4	.232
Cr, mg/dL*	1.0 (0.9–1.3)	0.9 (0.8–1.4)	1.0 (0.9–1.3)	.429
Medication, % (n)				
Beta-blocker	95% (104)	94% (58)	96% (46)	.605
ACE-I/ARB	96% (105)	95% (59)	96% (46)	.868
Spironolactone	76% (84)	74% (46)	79% (38)	.241
Furosemide	82% (90)	82% (50)	81% (40)	.442
Digoxine	40% (44)	42% (26)	37% (18)	.136
Nitrate	28% (31)	31% (19)	25% (12)	.347
Amiodarone	36% (40)	35% (22)	38% (18)	.229
Oral anticoagulation‡	25% (28)	27% (17)	23% (11)	.162

BSA, body surface area; BMI, body mass index; NYHA, New York Heart Association functional class; CRT-D, biventricular device combined with a defibrillator; LBBB, left bundle branch block; Hb, hemoglobin; Cr, creatinine; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
*Median (interquartile range).
†Chronic or paroxysmal atrial fibrillation.
‡Warfarin or novel agents (dabigatran, apixaban, or rivaroxaban).

in MR and slight improvement in mitral geometry which did not reach statistical significance.

Functional Improvement in RER Groups

The association of the improvement in NYHA functional class based on RER is demonstrated in Fig. 1A. Functional improvement was observed more frequently in patients with RER (n = 37 vs n = 21), whereas patients without RER were more likely to have NYHA functional class unchanged or worsened (n = 41 vs n = 11) after CRT (Pearson chi-square = 20.268; $P < .001$). In addition, although the baseline mean NYHA functional classes were similar (2.9 ± 0.6 vs 2.8 ± 0.7; $P = .683$), patients with RER showed a significant functional improvement (follow-up NYHA functional classes 1.9 ± 0.7 vs 2.5 ± 0.9; $P = .002$) compared with patients without RER at 6 months.

Association of RER With LV Reverse Remodeling

Comparison of the LV remodeling parameters in RER groups revealed that although the mean baseline LVESV values were similar (157.7 ± 49.8 mL vs 156.4 ± 51.4 mL; $P = .865$), follow-up mean LVESV values were significantly lower

Table 2. Change in Functional Status, Electrocardiographic, and Echocardiographic Parameters in Overall Population and in Groups Based on Reversed Electrical Remodeling (RER)

	Overall (n = 110)			RER− (n = 62)			RER+ (n = 48)		
	Baseline	Follow-Up	P Value	Baseline	Follow-Up	P Value	Baseline	Follow-Up	P Value
NYHA III/IV, % (n)	64% (71)	35% (38)	.014	60% (37)	45% (28)	.031	71% (34)	21% (10)	.002
Intrinsic QRS, ms	160.5 ± 20.9	161.6 ± 21.3	.242	158.8 ± 21.8	166.6 ± 21.3	<.001	162.7 ± 19.6	155.0 ± 19.7	<.001
LVESV, mL	157.0 ± 50.5	138.9 ± 51.1	<.001	156.4 ± 51.4	143.8 ± 53.6	<.001	157.7 ± 49.8	132.6 ± 47.5	<.001
LVEDV, mL	212.6 ± 57.9	197.4 ± 56.9	<.001	209.1 ± 57.5	198.8 ± 57.7	.001	217.1 ± 58.7	195.6 ± 56.4	<.001
LVEF, %	26.5 ± 5.7	29.8 ± 7.4	<.001	26.0 ± 5.8	28.1 ± 7.4	.003	27.2 ± 5.4	32.0 ± 6.9	<.001
EROA, cm²	0.24 ± 0.14	0.23 ± 0.11	.162	0.22 ± 0.11	0.29 ± 0.15	.001	0.21 ± 0.11	0.16 ± 0.10	.001
RegV, mL	30.7 ± 17.3	29.1 ± 14.8	.276	28.9 ± 15.0	36.5 ± 18.5	<.001	29.5 ± 14.6	22.2 ± 12.1	<.001
TA, cm²	3.98 ± 0.85	3.95 ± 0.86	.709	3.7 ± 0.7	3.8 ± 0.8	.029	4.3 ± 0.8	3.9 ± 0.9	.004
TD, cm	2.0 ± 0.4	1.9 ± 0.4	.788	1.9 ± 0.4	2.0 ± 0.4	.032	2.0 ± 0.5	1.9 ± 0.4	.010

EROA, effective regurgitant orifice area; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association functional class; RegV, regurgitant volume; A, tenting area; TD, tenting distance.
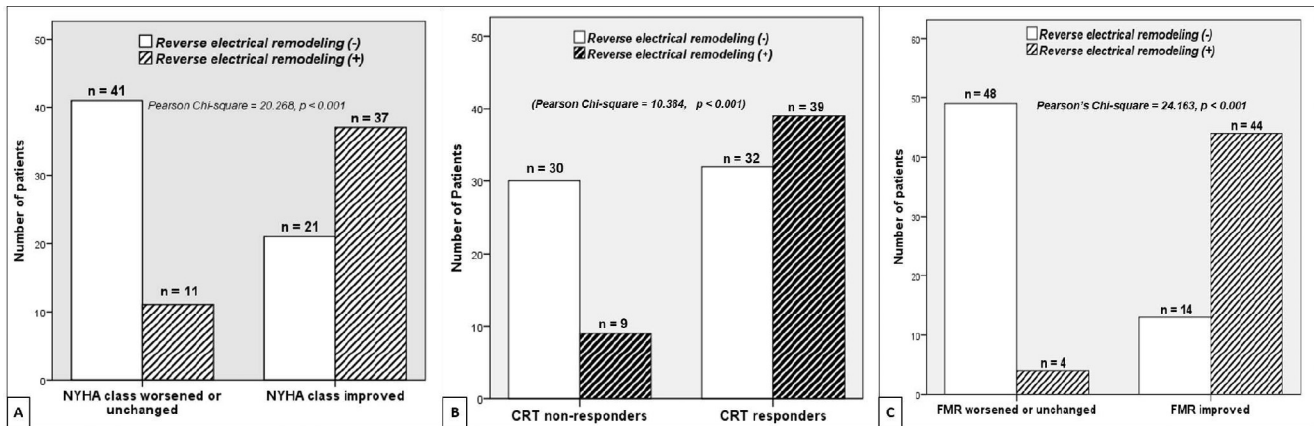
Fig. 1. Bar charts demonstrating the association between reversed electrical remodeling (RER) and functional, echocardiographic, and mitral regurgitation (MR) response at follow-up. (A) Functional response (≥1-degree improvement in New York Heart Association [NYHA] functional class) was observed more frequently in patients with RER, whereas patients without RER seemed to have a worsened or unchanged NYHA functional class ($P < .001$). (B) Cardiac resynchronization therapy (CRT) response was more frequently observed in patients with RER, whereas CRT nonresponse was more pronounced in patients without RER ($P < .001$). (C) MR response (reduction in RegV) was more frequently observed in patients with RER, whereas patients without RER seemed to have worsened or unchanged FMR at 6 months ($P < .001$).

(132.6 ± 47.5 mL vs 143.8 ± 53.6 mL, $P = .025$) and the mean changes in LVESV were significantly higher (25.0 ± 15.4 mL vs 12.5 ± 23.1 mL; $P = .002$) in patients with RER (Supplemental Fig. 1A). Similarly, mean baseline LVEF values were similar ($26.0 \pm 5.8\%$ vs $27.2 \pm 5.4\%$; $P = .280$), but mean follow-up LVEF was significantly higher ($32.0 \pm 6.9\%$ vs $28.1 \pm 7.4\%$; $P = .007$) and the mean change in LVEF higher ($4.7 \pm 3.8\%$ vs $2.1 \pm 5.4\%$; $P = .005$) in patients with RER compared with patients without RER (Supplemental Fig. 1B). The relationship between CRT response and RER is demonstrated with a clustered bar chart in Fig. 1B, revealing that presence of RER was associated with CRT response, whereas the absence of RER was associated with CRT nonresponse (Pearson chi-square = 10.384; $P < .001$).

Impact of RER on MR Severity and Mitral Geometry

A total of 58 patients (44 patients with RER vs 14 patients without RER) were found to have reduction in RegV at 6 months, whereas 52 patients (4 patients with RER vs 48 patients without RER) had no change or increase in MR after CRT (Pearson chi-square = 24.163; $P < .001$), as shown in Fig. 1C. The extent of change in the native QRS duration compared with the baseline QRS duration (ie, ΔQRS) showed a significant linear correlation with ΔRegV ($r = 0.513$; $P < .001$) and ΔTA ($r = 0.349$; $P < .001$) after CRT (Supplemental Fig. 2).

Predictors of Prognosis and MR Improvement

Among the several electrocardiographic parameters tested in the univariate Cox proportional hazard model for prediction of survival; statistically significant variables (P values <.05; paced QRS duration and RER) were entered into the multivariate analysis to determine the independent predictors. RER (HR 1.026, 95% CI 1.014–1.039; $P = .043$) was found to independently predict all-cause death. To define the

independent predictors of combined death/hospitalization, statistically significant variables in the univariate model (baseline QRS duration, paced QRS duration, and RER) were tested by means of multivariate Cox regression. Paced QRS duration (HR 1.012, 95% CI 1.005–1.019; $P = .048$) and RER (HR 2.071, 95% CI 1.208–4.910; $P = .028$) independently predicted event-free survival during the overall follow-up (Table 3).

Table 4 presents the logistical regression analyses for prediction of reduction in RegV (MR response) after CRT. Significant variables ($P < .05$) in the univariate model (paced QRS duration, RER, baseline LVESV, and baseline TA) were entered in the multivariate analysis. RER (HR 1.103, 95% CI 1.007–1.208; $P = .023$) and baseline TA (HR 2.011, 95% CI 1.268–2.754; $P = .014$) were the independent predictors of MR improvement after CRT.

Estimation of survival and event-free survival based on RER were separately analyzed by means of Kaplan-Meier method, as shown in Fig. 2. Presence of RER showed statistical significance for prediction of survival (free from all-cause death: log rank 3.938; $P = .047$) and event-free survival (free from combined death/hospitalization: log rank 6.066; $P = .014$) during the mean follow-up of 18 ± 3 months after CRT implantation.

Discussion

In the present study, we evaluated the clinical impact of narrowing of the intrinsic QRS duration after CRT on the echocardiographic and clinical outcomes. According to the main findings of the study, a narrowed intrinsic QRS duration compared with the baseline was strongly associated with higher incidence of functional improvement, greater CRT response, and reduced MR severity. Moreover, narrowing of the native QRS duration was a predictor of MR response, hospitalization, and death during the follow-up.

Table 3. Cox Proportional Hazard Model for Prediction of All-Cause Mortality and Combined Death and Hospitalization According to Univariate and Multivariate Analyses

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
Death from all causes						
Baseline QRS duration	0.987	0.963–1.011	.272			
LBBB morphology	0.658	0.189–2.293	.511			
Paced QRS duration	1.033	1.012–1.054	.036	0.456	0.085–2.440	.359
Follow-up intrinsic QRS duration	1.000	0.979–1.021	.641			
Reverse electrical remodeling	2.180	1.356–3.504	.026	1.026	1.014–1.039	.043
Combined death and hospitalization						
Baseline QRS duration	1.125	1.082–1.168	.012	0.842	0.416–1.706	.112
LBBB morphology	1.430	0.755–2.709	.272			
Paced QRS duration	1.026	1.014–1.039	.022	1.012	1.005–1.019	.048
Follow-up intrinsic QRS duration	0.996	0.983–1.010	.587			
Reverse electrical remodeling	2.245	1.150–4.382	.018	2.071	1.208–4.910	.028

HR, hazard ratio; CI, confidence interval; LBBB, left bundle branch block.

Table 4. Univariate and Multivariate Logistic Regression Analyses to Determine Independent Predictors of Improvement in Mitral Regurgitation (MR Response)

	OR	95% CI	P Value
Univariate analysis			
Baseline QRS duration	1.009	0.991–1.028	.318
Paced QRS duration	1.040	1.023–1.057	.032
Follow-up intrinsic QRS duration	1.044	0.977–1.117	.201
RER	2.651	1.112–6.309	.032
Baseline LVESV	1.012	1.005–1.019	.028
Baseline LVEF	0.767	0.327–1.798	.541
TA	1.916	1.228–2.290	.012
Multivariate analysis			
Paced QRS duration	0.996	0.985–1.007	.415
RER	1.103	1.007–1.208	.023
Baseline LVESV	1.966	0.410–9.428	.398
TA	2.011	1.268–2.754	.014

OR, odds ratio; other abbreviations as in Tables 1 and 2.

CRT has been primarily accepted as an electrical therapy that aims to restore the synchronicity of the conduction system in the failing heart.[18] The evidence arising from RV-pacing studies[19] supports that deterioration of intraventricular conduction by inducing iatrogenic LBBB further affects LV systolic dysfunction and can be reversed with the use of biventricular pacing.[20] In addition, complete restoration of the electrical remodeling in a patient with LBBB resulted in superresponse to CRT, as shown by Dizon et al,[21] suggesting that reversal of electrical remodeling is the main target of biventricular pacing in heart failure.

CRT-induced RER has been addressed in several previous studies. Narrowing of the intrinsic QRS duration by CRT was mostly evaluated for favorable structural changes and prediction of CRT response. Although Stockburger et al did not find any association between structural and electrical remodeling,[22] a study from Boriani et al suggested that the extent of QRS shortening by CRT was a determinant of reduction in LVESV.[6] Similarly, Yang et al found that narrowing of the intrinsic QRS complex correlated with CRT response.[5]
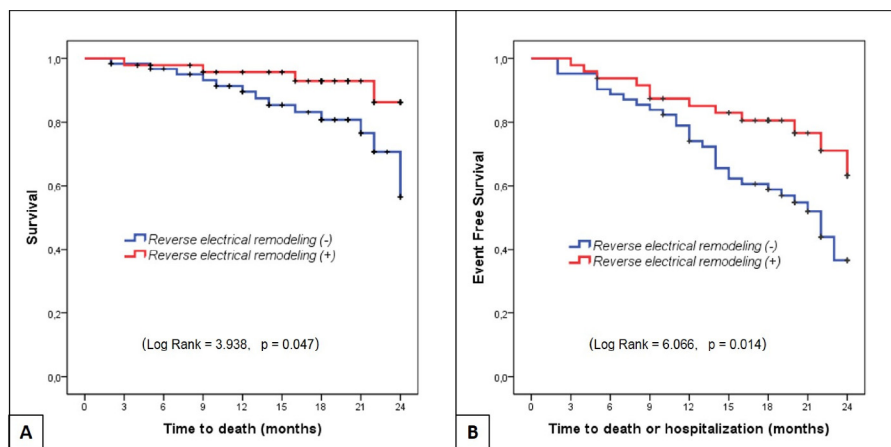
Fig. 2. Kaplan-Meier curves generated for estimation of the study end-points during a mean follow-up of 18 ± 3 months. (A) Estimation of survival (free from all-cause death: log rank = 3.938; $P = .047$). (B) Estimation of event-free survival (free from combined death/hospitalization: log rank = 6.066; $P = .014$).

However, there is no uniform definition of RER in the literature. Tereshenko et al accepted ≥10 ms of QRS narrowing as an index of RER and found an association with decreased mortality.[23] A study by Yang et al suggested that regression of the fragmented QRS complex interval was associated with improved electrical conduction that resulted in beneficial outcomes after CRT.[24] We observed that even minor alterations in the native QRS duration correlated with significant echocardiographic changes after CRT. Therefore, in the present study we used the absolute QRS narrowing as an index of RER to correlate with clinical outcomes.

Consistently with the recent studies, our study once again confirmed that the presence of RER is strongly associated with increased functional and echocardiographic response after CRT. However, we investigated the effect of RER beyond the extent of LV reverse remodeling. We also correlated RER with important prognostic variables such as improvement in MR and reduction in death and hospitalization. Reversal of the intrinsic electrical dyssynchrony induced by CRT is the suggested mechanism of action that triggers the reversal of both mechanical dyssynchrony and LV remodeling, leading to favorable clinical and echocardiographic outcomes after CRT.

Comparison of the baseline characteristics in our study population revealed that traditional CRT response predictors,[25] such as female sex, baseline QRS duration, and LBBB morphology, did not differ in RER groups. However, patients with RER had nonischemic cardiomyopathy more frequently and tended to have narrower paced QRS durations, which may have influenced the results of the study. According to a report by Hsing et al,[26] paced QRS and the CRT-induced QRS change predicted favorable clinical outcomes and LV reverse remodeling. Similarly, QRS narrowing as indexed to baseline was significantly associated with reversed LV remodeling after CRT, as reported by Rickard et al.[20] Lecoq et al evaluated CRT response in 139 patients and noted that QRS narrowing was a determinant of CRT response.[3] We achieved similar results in our study regarding the importance of paced QRS duration after CRT. Based on the regression analyses, paced QRS duration was found to be a univariate predictor of both death/hospitalization and MR response, which necessitates further studies to confirm these findings.

In line with the major CRT trials, we had an overall CRT response rate of 65%. Both the overall population and the RER groups showed marked reduction in mean NYHA functional class and marked improvements in LV remodeling parameters (LVESV, LVEDV, and LVEF). In contrast, reduction in MR severity and improvement in mitral valve geometry were observed only in the group of patients with RER. The MR parameters assessed in the study (RegV, EROA, TA, and TD) significantly worsened in patients without RER, although they mildly (statistically insignificantly) improved in the overall population. Overall, 58 patients (53%) were MR responders, which consisted of 44 patients with RER and 14 patients without RER. Corresponding MR response rates were 92% vs 23% in the RER groups, which clarified the role of intrinsic QRS narrowing on MR severity after CRT.

Predictors of MR improvement after CRT have been widely investigated recently. It is important to differentiate functional MR from organic or ischemic MR both of which involve distinctive mechanisms. CRT has been shown to positively interact with and ameliorate the imbalance between the tethering forces (due to papillary muscle dyssynchrony and/or annular dilatation) and the impaired closing forces (due to reduced LV contractility and/or LV dyssynchrony) that were suggested as the underlying mechanisms of MR in patients with heart failure. Ypenburg et al reported that baseline LV mechanical dyssynchrony was associated with improvement in MR after CRT.[9] Sitges et al suggested that excessive remodeling of the LV and mitral valve predicted an unfavorable MR response after CRT.[8] Likewise, we found that baseline LVESV was a univariate predictor of MR response, whereas baseline TA was an independent predictor of MR response according to multivariate analysis. Because previous studies did not provide sufficient data regarding the influence of intrinsic QRS narrowing on MR improvement, the present study is among the first to focus on the correlation of ΔQRS with the reduction in RegV and in TA. Moreover, CRT-induced RER has never previously been suggested as a predictor of MR response.

According to the results of the present study, favorable effects of CRT on MR improvement in patients with RER might be explained by several mechanisms. First, amelioration of the native conduction after CRT results in improvement in LV remodeling parameters that subsequently leads to a decrease in MR severity as a result of smaller LV volumes. Second, improvements in global LV remodeling in patients with RER might favorably interact with the local remodeling parameters acting on the mitral apparatus, such as reduction in the mitral annular area, TA, and TD. Third, reversal of the mechanical dyssynchrony, especially at the papillary muscle level, is a mechanism for MR improvement after CRT induced by the reversal of the intrinsic electrical dyssynchrony.

Among the predictors of death and hospitalization following CRT, we achieved some "classic" and "novel" results in the present study. According to univariate analysis, traditional variables,[25,27,28] including the baseline and the paced QRS durations, tended to affect prognosis after CRT, as expected. These findings were in line with previous meta-analyses investigating the predictors of mortality and morbidity after CRT.[29,30] A unique feature of the present study is that narrowing of the intrinsic QRS duration after CRT is proposed as an independent predictor of both survival and event-free survival by multivariate analysis.

Study Limitations

The main limitation of the study is that the study population consists of patients treated in a single center with a relatively small sample size. The overall follow-up period was 18 ± 3 months with a wide variation (range 1–24 months) to reach the study end points. Therefore, assessment of functional improvement, CRT response, and MR reduction was

done at 6 months, which is a generally accepted time interval to assess clinical and echocardiographic response to CRT. Patients who died within the 1st 6 months (n = 3; 1 with RER and 2 without RER) were included in the analyses with their baseline values. In addition, the absence of long-term echocardiographic data and of the association with prognosis during the overall follow-up might also be an area of criticism.

Any method for quantification of MR involves some drawbacks. Although the addition of vena contracta and jet area assessment would have increased accuracy, the PISA method that we used in the present study to assess RegV is the criterion standard in current guidelines. In addition, 3-dimensional assessment by tenting volume analysis would be more precise, because the evaluation of the mitral valve remodeling is anatomically challenging. Another possible limitation is that there was a significant overlap between the patients with reduction in the paced and in the native QRS durations. The differentiation of a coexistence or a cause-effect relationship must be established in further studies. Finally, long-term clinical data on ventricular arrhythmias or need for transplant/assist device would be more comprehensive, because we focused only on major clinical end points, such as improvement in NYHA functional class, hospitalization, and death.

Conclusion

Reversed electrical remodeling by means of narrowing of the intrinsic electrocardiographic QRS duration after CRT has clinical and prognostic implications. A narrowed intrinsic QRS interval than the baseline is associated with improved functional status, higher CRT response, reduced MR, and favorable prognosis after CRT. The results of the present study suggest that the assessment of the native conduction should be a part of routine clinical follow-up of patients after CRT. Further randomized studies are needed for translation of our findings into clinical practice with algorithms including RER assessment for early prediction of prognosis after CRT.

Disclosures

None.

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2016.04.001.

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