Regression of Fragmented QRS Complex: A Marker of Electrical Reverse Remodeling in Cardiac Resynchronization Therapy

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Background: Fragmented QRS (fQRS) marks inhomogeneous activation and asynchronous cardiac contraction. It has been proved that cardiac resynchronization therapy (CRT) could reverse geometrical remodeling as well as correct electrical dyssynchrony. We aimed to investigate whether fQRS changed corresponding to the therapeutic response to CRT.

Methods: Patients who underwent de novo CRT implantation previously and had ≥ 1 follow-up between August 2012 and September 2013 in our hospital were investigated. Intrinsic electrocardiogram was recorded and fQRS in any lead was calculated. Response to CRT was defined as absolute improvement in left ventricular ejection fraction by $\geq 10\%$ or by improvement > 1 New York Heart Association class and without heart failure hospitalization.

Results: A total of 75 patients (48 male, mean ages, 61 ± 9 years) were included in this study. At a median follow-up of 13 months, 57 patients had response to CRT. Responders had narrowed QRS (from 167 ± 23 ms to 158 ± 19 ms, $P = 0.003$) and reduced fQRS post-CRT. Nonresponders had QRS prolonging (from 151 ± 26 ms to 168 ± 16 ms, $P = 0.033$) and increase in fQRS. Eleven of 12 patients with reduced fQRS were responders and 8 of 12 with increased fQRS were nonresponders. Both changes in QRS and fQRS correlated strongly with CRT response ($r = 0.389$, $P = 0.001$ and $r = 0.403$, $P = 0.000$, respectively). Reduction of fQRS in ≥ 1 leads had high specificity (95%) in association to responders, though in low sensitivity (19%).

Conclusions: The changes in fQRS associated with therapeutic response to CRT. Regression of fQRS could be a marker of electrical reverse remodeling following CRT.

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chronic heart failure; cardiac resynchronization therapy; fragmented QRS complex; electrical remodeling; response

The benefits of cardiac resynchronization therapy (CRT) have been established by serial pivotal clinical trials, including improving quality of life, modifying adverse remodeling, as well as reducing hospitalization and mortality.^{1–4} Hence, CRT has been taken as a standard management in systolic heart failure with evidence of asynchrony.^{5,6} The mechanism for CRT is to correct underlying

electrical dyssynchrony. There are reports that the electrical abnormalities are also reversed following CRT, manifesting as QRS shortening after device initiation.⁷ Increasing evidences indicate that QRS narrowing is a reflection of electrical resynchronization induced by biventricular pacing.

In recent years, a multiple deflection of QRS on surface electrocardiogram (ECG), fragmented

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QRS complex (fQRS), has been proved to be associated with inhomogeneous ventricular activation and asynchronous cardiac contraction.⁸⁻¹⁰ The fQRS could predict arrhythmic event as well as sudden cardiac death in a variety of disease states, including ischemic heart disease, idiopathic dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, left ventricular (LV) noncompaction cardiomyopathy, and Brugada syndrome.¹¹⁻¹⁶ In addition, fQRS is also investigated in patients with heart failure undergoing CRT. It was reported that the number of leads with fQRS negatively associated with the therapeutic response to CRT.^{17,18}

Given the nature of electrical therapy conferred by CRT, we postulated that fQRS may be changed as heart failure improved or worsened following resynchronization therapy. Until now, there is no report concerning this issue. In this study, we aimed to test the hypothesis that the number of leads with fQRS would be changed according to patient's response to CRT.

PATIENTS AND METHODS

Study Population

Patients who had ≥ 1 follow-up between August 2012 and September 2013 in our hospital were investigated. For inclusion in the final cohort, all patients had baseline New York Heart Association (NYHA) class II-IV, sinus rhythm, QRS duration ≥ 120 ms, LV end-diastolic dimension (LVEDD) ≥ 55 mm, LV ejection fraction (LVEF) $\leq 35\%$ on optimal medical therapy, and had a de novo CRT implant in our center previously. Those with right ventricular pacing upgraded to CRT, pacer dependency, and/or atrial fibrillation were excluded. Medications were recorded before the operation and titrated by outpatient physicians postimplantation. In instances where more than one study was obtained, data of the last interview was selected. Follow-up data were acquired beyond the first 3 months postoperation. Response to CRT was defined as an absolute improvement in LVEF by $\geq 10\%$ from baseline or by improvement > 1 NYHA class and without heart failure hospitalization.^{19,20}

Device Implantation

CRT implantations were performed successfully by transvenous approach in the majority of

patients. Lateral or posterolateral cardiac vein was chosen preferably for LV lead. Right atrial lead was placed in the right auricle and right ventricular lead in the right ventricular apex. The pulse generators were implanted in the left subclavicular region. In case that transvenous implantation failed, a minimally invasive surgery was given to fix LV lead on the LV epicardium. The atrioventricular (AV) and ventricular-ventricular interval was routinely programmed to a sensed AV delay of 100 ms, paced AV delay of 130 ms, and biventricular pacing simultaneously. Optimization based on echocardiography was given to patients without improvement in NYHA class and LVEF at 3-6 months follow-up.

Electrocardiogram Assessment

The resting 12-lead surface ECGs were recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV preoperation, instantaneously post-CRT, and at follow-up. At follow-up, the device was programmed to pacing off briefly to obtain spontaneous ECG. The duration of QRS complex was described as the widest interval in any lead recorded digitally and checked manually.²¹ QRS duration pre-CRT, post-CRT, and changes in QRS duration (Δ QRS; pre-CRT QRS duration minus post-CRT QRS duration) was evaluated. Fragmentation of QRS complex (fQRS) was defined as the presence of > 2 R waves, > 2 notches in the R wave, or > 2 notches in the downstroke or upstroke of the S wave.^{8,22} Change in the number of leads with fQRS (Δ fQRS) was calculated as the numbers of fQRS in any of 12 leads pre-CRT subtract the numbers on unpaced ECG. The true left bundle branch block (TLBBB) was diagnosed when QS or rS morphology in lead V₁, monophasic R wave in leads V₆ and VI, and with a mid-QRS notching or slurring in at least two of leads V₁, V₂, V₅, V₆, VI, and aVL.²³ (Fig. 1). All ECGs were analyzed independently by two experienced physicians who were blinded to the clinical and echocardiographic data. The concordance between the two readers was 98%. Any disagreement was settled by mutual consent.

Echocardiography Analysis

Transthoracic echocardiography was performed before CRT and at follow-up by commercially available system (Vivid 7; GE Medical

Figure 1. The ECGs of a responder with TLBBB and fragmented QRS complex (fQRS). fQRS has been indicated by black arrow. (A) The ECG recorded pre-CRT. fQRS presented in leads III, aVL, aVF, and V₆. (B) The ECG recorded 6 months post-CRT. fQRS presented in leads III and aVF.

Systems-Americas, Waukesha, WI, USA). Images were obtained by using a 2.5-MHz broadband transducer at a depth of 16 cm in the parasternal or apical views. The diameter of left atrium and LVEDD were measured from parasternal long-axis view according to the recommendation of American Society of Echocardiography.²⁴ LVEF was assessed by using biplane Simpson's method in a two- and four-chamber apical view.

Statistical Analysis

All data were analyzed by using SPSS statistical software (version 18.0; SPSS Inc., Chicago, IL,

USA). Continuous variables were expressed as mean $\pm$ SD. Categorical variables were presented as numbers and/or percentages. Comparisons in continuous data were by independent sample's *t*-test for parametric variables, by Mann-Whitney U test for nonparametric variables, and by chi-square test in dichotomous variables. Correlation of Δ fQRS and Δ QRS with other variables were conducted by Pearson correlation analysis or by Spearman correlation analysis as appropriate. A receiver operating characteristic (ROC) curve was depicted to reveal the best cutoff number of lead with changes in fQRS to the therapeutic response to CRT. All statistical analysis was

Table 1. Demographic and Clinical Characteristics of Study Groups

	Total (n = 75)	Rs (n = 57)	NRs (n = 18)	P Value
Age (years)	61 ± 9	61 ± 8	61 ± 12	NS
Male n (%)	48 (64%)	36 (63%)	12 (67%)	NS
Etiology n (%)				NS
ICM	17 (23%)	10 (18%)	7 (38%)	
Non-ICM	58 (77%)	47 (82%)	11 (61%)	
Mean NYHA class	2.9 ± 0.7	2.8 ± 0.6	3.3 ± 0.8	0.013
TLBBB n (%)	36 (48%)	31 (54%)	5 (28%)	0.061
QRS duration (ms)	163 ± 24	167 ± 23	151 ± 26	0.013
SBP (mmHg)	112 ± 14	112 ± 15	112 ± 11	NS
DBP (mmHg)	69 ± 11	69 ± 12	68 ± 8	NS
Hs-CRP (mg/L)	3.86 ± 4.27	3.69 ± 4.04	4.41 ± 5.00	NS
NT-proBNP (pmol/L)	2302 ± 2575	1893 ± 1520	3506 ± 4264	0.021
Hb (g/L)	138 ± 15	138 ± 15	138 ± 16	NS
Medication n (%)				
β-Blocker	69 (92%)	53 (93%)	16 (89%)	NS
ACEI/ARB	54 (72%)	44 (77%)	10 (56%)	NS
Spirolactone	65 (87%)	51 (89%)	14 (78%)	NS

Rs = responders; NRs = nonresponders; ICM = ischemic cardiomyopathy; non-ICM = nonischemic cardiomyopathy; NYHA = New York Heart Association; TLBBB = true left bundle branch block; SBP = systolic blood pressure; DBP = diastolic blood pressure; Hs-CRP = high sensitive C-reactive protein; NT-proBNP = N-terminal pro-brain natriuretic peptide; Hb = hemoglobin; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Table 2. Baseline and Follow-Up Data between Responders and Nonresponders

Variables	Total (n = 75)	Rs (n = 57)	NRs (n = 18)	P Value
Baseline data				
Mean NYHA class	2.9 ± 0.7	2.8 ± 0.6	3.3 ± 0.8	0.013
LAD (mm)	42 ± 8	42 ± 8	45 ± 6	NS
LVEDD (mm)	72 ± 10	71 ± 9	75 ± 11	NS
LVEF (%)	26 ± 6	26 ± 6	27 ± 7	NS
QRS pre-CRT (ms)	163 ± 24	167 ± 23	151 ± 26	0.013
QRS post-CRT (ms)	160 ± 18	158 ± 19	168 ± 16	0.039
ΔQRS (ms)	3 ± 27	9 ± 22	-17 ± 31	0.000
Mean fQRS	0.7 ± 1.4	0.7 ± 1.5	0.6 ± 1.1	NS
Follow-up data				
Mean NYHA class	1.9 ± 0.8	1.7 ± 0.6	2.9 ± 0.6	<0.001
LAD (mm)	40 ± 7	38 ± 7	46 ± 7	<0.001
LVEDD (mm)	64 ± 12	61 ± 11	73 ± 11	<0.001
LVEF (%)	40 ± 12	43 ± 11	30 ± 8	<0.001
Mean fQRS	0.8 ± 1.3	0.5 ± 1.1	1.4 ± 1.5	0.003

Rs = responders; NRs = nonresponders; LAD = left atrium diameter; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; mean fQRS = mean number of leads with fQRS; ΔQRS = changes in QRS duration pre- and post-CRT.

two tailed and a P value <0.05 was considered significant.

Ethics

This study complied with Declaration of Helsinki. The protocol was approved by Institute Ethics Board. All patients had given their informed consent.

RESULTS

Patient Population

A total of 75 patients (48 male, mean ages, 61 ± 9 years) were included in this study, with 36 (48%) had TLBBB and 17 (23%) had ischemic cardiomyopathy. Baseline characteristics of the study population were listed in Table 1. Most of patients had CRT devices implanted transvenously,

Figure 2. The distribution of changes in the number of leads with fragmented QRS complex (fQRS).

only two with exceptions. LV lead was placed in the lateral/posterolateral tributaries in 54 patients (72%). At a median follow-up of 13 months (6–36 months), 57 patients had response to CRT.

Comparison of Clinical and Echocardiographic Parameters between Responders and Nonresponders

In comparison with responders, nonresponders had advanced NYHA class (3.3 ± 0.8 vs 2.8 ± 0.6 , $P = 0.013$), higher plasma NT-proBNP (pmol/L; 3506 ± 4264 vs 1893 ± 1520 , $P = 0.021$), and less TLBBB (28% vs 54%, $P = 0.061$). No significant differences were observed in other baseline characteristics. At follow-up, responders had significant improvement in NYHA class (from 2.8 ± 0.6 to 1.7 ± 0.6 , $P < 0.001$), LVEF (from $26\% \pm 6\%$ to $43\% \pm 11\%$, $P < 0.001$), and LVEDD (from 71 ± 9 mm to 61 ± 11 mm, $P < 0.001$). No significant improving in functional or echocardiographic data observed in nonresponders (Table 2).

Comparison of ECG Parameters between Responders and Nonresponders

Comparing by mean number of leads with fQRS, responders had a marginal significant reduction (0.7 ± 1.5 at baseline vs 0.5 ± 1.1 at follow-up, $P = 0.046$), while nonresponders had significant increase (0.6 ± 1.1 at baseline vs 1.4 ± 1.5 at follow-up, $P = 0.011$) post-CRT. The difference in mean fQRS between responders and nonresponders was insignificant (0.6 ± 1.1 in nonresponders vs 0.7 ± 1.5 in responders, NS) at baseline, but notably (1.4 ± 1.5 in nonresponders vs 0.5 ± 1.1 in responders, $P = 0.003$) at follow-up (Table 2).

QRS duration was much shorter in nonresponders preimplantation (151 ± 26 ms vs 167 ± 23 ms, $P = 0.013$). After initiation of biventricular pacing, QRS was broadened from 151 ± 26 ms to 168 ± 16 ms ($P = 0.033$) in nonresponders, with a mean increase of 17 ± 31 ms. In responders, however, QRS duration was decreased from 167 ± 23 ms to 158 ± 19 ms ($P = 0.003$), the mean reduction was 9 ± 22 ms.

Table 3. Baseline and Changes in the Number of Leads with fQRS and Response to CRT

Baseline fQRS	Δ fQRS	NRs	Rs	Total
N	-3	4	0	4
N	-2	0	1	1
N	-1	3	2	5
N	0	7	39	46
Y	-2	1	0	1
Y	-1	0	1	1
Y	0	2	3	5
Y	1	1	6	7
Y	2	0	3	3
Y	3	0	2	2
Total		18	57	75

Baseline fQRS: N = no fQRS at baseline; Y = have fQRS at baseline; Δ fQRS = changes in number of leads with fQRS; (-), increase in fQRS; (+), reduction in fQRS; NRs = non-responders; Rs = responders.

Table 4. Correlation between Changes of fQRS and QRS Duration with Other ECG Variables

Variables	Δ fQRS		Δ QRS	
	r	P	r	P
QRS pre-CRT	0.197	0.091	0.747	0.000
QRS post-CRT	-0.045	0.703	-0.488	0.000
TLBBB	0.291	0.011	0.325	0.004
Δ QRS	0.206	0.076		
Response	0.403	0.000	0.389	0.001

Δ fQRS = changes in number of leads with fragmented QRS; Δ QRS = changes in QRS duration pre- and post-CRT; QRS pre-CRT = QRS duration measured preimplant; QRS post-CRT = QRS duration measured postimplant; LBBB = left bundle branch block.

Change in the Number of Leads with fQRS

fQRS in ≥ 1 lead was found in 19 patients at baseline and in 25 patients at follow-up. The distribution of change in the number of leads with fQRS was shown in Figure 2. Eleven of 12 patients (91.7%) with reduction in fQRS had response to CRT and 8 of 12 patients (66.7%) with increase in fQRS were nonresponders (Table 3).

Correlation analysis

As shown in Table 4, there was a positive correlation between Δ fQRS and TLBBB, QRS pre-CRT, and Δ QRS, but with the strongest correlation with response to CRT ($r = 0.403$, $P = 0.000$). Δ QRS also had a positive correlation with TLBBB, QRS pre-CRT, and therapeutic response to CRT ($r =$

0.389, $P = 0.001$). A positive but weak correlation was revealed between Δ fQRS and Δ QRS ($r = 0.206$, $P = 0.076$; Fig. 3).

ROC Curve

ROC curve was performed on the number of leads with change in fQRS to patient's response to CRT. The area under curve was 0.725 (95% CI 0.58–0.87, $P = 0.004$). Reduction in ≥ 1 lead with fQRS associated with response to CRT in high specificity (95%) though in low sensitivity (19%).

DISCUSSION

Reverse remodeling in cardiac geometry has been proved in lines of basic researches and clinical trials regarding to CRT. In contrast, even emerging as an electrical therapy, reversal of electrical abnormality has been less investigated. In this study, we attempted to test how fQRS would be changed after a period of biventricular pacing, and sought to explore the correlation between instant changes in QRS duration and relatively long-term changes in fQRS. We found that both the indices associated with CRT response strongly. Responders manifested acute QRS shortening and experienced reduction in fQRS at follow-up, while nonresponders had broadened QRS and increased fQRS during biventricular pacing. This supports the hypothesis that modification of electrical abnormality is progressively continuing by CRT. As a reflection of long-term electrical remodeling, reduction of fQRS in ≥ 1 lead had high specificity (95%) in association to favorable response. Regression of fQRS would be a new marker of electrical reverse remodeling in resynchronization therapy.

CRT is an electrical therapy with the purpose to rectify underlying electrical dyssynchrony. Wide QRS interval predicts asynchronous LV activation and poor prognosis in heart failure patients.^{25,26} Thus, broader QRS complex provides basis for more effective treatment of CRT and usually associates with beneficial outcomes.^{27,28} Previous studies proved that QRS shortening postimplantation accompanied favorable response irrespective of new implantation or upgrading to CRT.^{7,29} In contrast, QRS widening associated with suboptimal response and even worsening in heart function.^{30,31} Our results, in consistent with other studies, demonstrated that the mean QRS duration was abbreviated in responders but prolonged

Figure 3. The relationship between changes in QRS duration and changes in fQRS.

in nonresponders. Alteration in Δ QRS had a close correlation with CRT response. Our findings further stand for the concept that QRS narrowing reflect the correction of electrical asynchrony, and predict the effectiveness of CRT.³²

Although QRS duration is a simple and available measurement in evaluation of electrical remodeling following CRT, great variation and overlap persists between responders and nonresponders.⁷ An optimal cutoff value for response prediction is also unavailable. Additionally, the early changes in QRS duration could not reflect the long-term changes in electrical synchronicity following resynchronization therapy. Although other ECG parameters including JT interval and PR interval had been investigated, but none of them proved to be more preponderance.³³ Thus, efforts to explore new marker of electrical remodeling are warranted.

In recent years, fragmentation of QRS complex resulting from myocardial ischemia, myocardial scars, and/or fibrosis, has been investigated widely and is considered to be associated with inhomogeneous ventricular activation.^{8–10,13,34} However, studies concerning fQRS in heart failure got

controversial results.^{18,22,35} In a study with 232 patients, Rickard et al. found that fQRS could not predict CRT response.²² In contrast, Celikyurt et al. reported that fQRS negatively associated with patient's response to CRT.¹⁷ We analyzed these studies and thought that the differences in patient selection and definition of fQRS underlay these conflicting conclusions. fQRS recorded in contiguous leads was calculated and a negative result was obtained in the prior research, while patients with LBBB were exclusively recruited and fQRS in any lead was counted, so the conclusion was positive in the latter study.

In this study, we sought to explore fQRS in a new aspect in labeling changes in electrical abnormalities during CRT, by assessing changes in fQRS and its relation to therapeutic response to CRT. For this purpose, we calculated fQRS in any of 12 leads. We found that patients with reduced fQRS had high odds of responders (91.7%), while increase in fQRS more possibly nonresponders (66.7%). Δ fQRS and Δ QRS changed in the same direction, both of the two parameters were associated with CRT response strongly. This

supports the postulation that Δ QRS reflect an early resynchronization imposed by CRT, while Δ fQRS might be the long-term result in electrical remodeling induced by CRT.

QRS duration and fQRS may be different in labeling ventricular dyssynchrony. This can be explained by the fact that the width of QRS complex is an overall timing of ventricular activation. The vector of regional abnormalities in activation and conduction may not be exposed by the width of QRS.³⁶ In striking contrast, fQRS predominantly represents local zigzag activation when impulse propagating around or through diseased myocardium. This multiple spike within QRS complex associated with intraventricular dyssynchrony.¹⁰ Thus, the presence of fQRS is a valuable adjunctive index to QRS interval in evaluating electrical disorders. Most importantly, we demonstrated that Δ fQRS represented a long-term effect on electrical remodeling imposed by CRT. Although the mean number of leads with fQRS was little of practical significance, actually, one can only evaluate an individual patient by their own ECG. As for small portion of patients presented with fQRS on baseline ECG and experienced changes in fQRS during CRT, regression of fQRS associated with beneficial response in high specificity (95%) but in low sensitivity (19%).

Need to be aware is variation also exhibited in Δ fQRS and CRT response. Four patients with increased fQRS had response to CRT and one with fQRS reduction was nonresponder. This may be explained by the disassociation between electrical and mechanical dyssynchrony, individual substrates, and heterogeneity of electrical asynchrony.^{37,38} The changes in fQRS associated with baseline QRS duration, TLBBB, as well as Δ QRS, factors relating to therapeutic responses to CRT, these indirectly supported that the alteration of fQRS associated with the effectiveness of resynchronization therapy. The mechanisms underlying changes in fQRS were still unknown. According to the literatures, patients with CRT experienced reverse remodeling in molecular level, such that apoptosis of myocytes, turnover of collagen, abnormal expression of genes, ionic channels, and proteins were also reversed.^{39–41} Improvement in regional activation, conduction, and contraction may be reflected by the regression of fQRS after resynchronization therapy.

Limitations

Our study has some limitations. First, this observational study was conducted in a single center and with small number of patients. Our patients had a wide variation in follow-up periods. To mitigate this variation, we got the follow-up data of ECG and echocardiography at the same time point. Besides, our patients had median follow-up of 13 months with the shortest visit of 6 months. So our results represent medium to long-term outcomes of CRT. Moreover, the ECGs were written with a filter setting of 0.08–40 Hz. This filtering might not be optimal in analyzing fQRS on surface ECG. But we compared the difference pre- and postbiventricular pacing in the same conditions. That might modify the shortcoming of low filter settings. In view of these limitations, our findings should be taken with cautions. However, we truly believe that our finding furthered our current comprehensions about electrical remodeling during CRT. Well-designed prospective studies are warranted to confirm our results in future.

CONCLUSION

The number of leads with fQRS changed in association to the therapeutic response to CRT. Regression of fQRS could be a marker of reversal of electrical dyssynchrony in resynchronization therapy.

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