QRS Fragmentation Outcome in Patients Receiving Cardiac Resynchronization Therapy

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Abstract

Background: Myocardial scar causes heterogeneous ventricular activation, which results in the fragmentation of QRS (f-QRS) complexes.

Objectives: The current study aimed to investigate the clinical and echocardiographic benefits of cardiac resynchronization therapy (CRT) implantation in patients with f-QRS versus the patients without it.

Patients and Methods: Eighty patients (40 with and 40 without f-QRS) who underwent CRT were enrolled and followed up for six months. The two groups were compared for the functional class, quality of life, echocardiography indices, arrhythmia burden, recurrent hospitalization and mortality before and after CRT implantation.

Results: The mean baseline left ventricular ejection fraction (LVEF), left ventricular end diastolic dimension (LVEDD) and left ventricular end systolic dimension (LVESD) in both groups were not different (P > 0.05). Improvements were observed in LVESD, LVEDD and LVEF in patients without f-QRS after CRT (P = 0.003). The functional class and mitral regurgitation (MR) severity improved in both groups. Before implantation, 36 (45%) and 27 (33.8%) patients had mild and moderate MR, respectively. Six months post implantation, 41 (51%) (17 cases with f-QRS) and 20 (25%) (11 cases with f-QRS) patients had mild and moderate MR, respectively (P = 0.003). Improvements in the MR severity and functional class were observed in both groups.

Conclusions: Regarding LVEF, LVESD, and LVEDD, a significant difference was observed in patients without f-QRS after CRT implantation compared to patients with f-QRS.

Keywords: QRS Fragmentation, Electrocardiography, Echocardiography, Cardiac Resynchronization Therapy, Mitral Regurgitation

1. Background

Electrical dyssynchrony is present when a wide QRS is evident on electrocardiography (ECG). In a subset of patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF), this dyssynchrony contributes to the pathophysiology of HF and is associated with negative remodeling and increased risk of clinical events, including mortality. In the majority of HF patients with evidence of dyssynchrony, cardiac resynchronization therapy (CRT) restores the appropriate timing of the cardiac contraction and thereby not only reduces cellular, hemodynamic and structural maladaptations of dyssynchrony, but also ultimately improves functional status, decreases hospitalization, and increases survival.

Slurring and changes in the morphology of the QRS complex are investigated since the 1960s. Das et al. (1) demonstrated that the presence of fragmented QRS (f-QRS) complexes was more common among patients with prior myocardial infarction and among patients with either right or left ventricular (LV) enlargement. The f-QRS, in particular late potentials, is investigated as a possible new tool to identify the high-risk cardiac population. Upon the analysis of the data obtained from an epicardial and endocardial mapping of the patients undergoing LV aneurysm incision, Pietrasik (2) demonstrated that a fragmented electrical activity was present in all patients with LV aneurysms. However, the patients with ventricular tachycardia had the fragmented electrical activity from a larger proportion of the endocardial border zone and had more prolonged electrogram in this zone than patients without ventricular tachycardia. It was proposed that the endocardial electrical activity mapping and detection of the fragmented activity was a useful tool for surgically guided therapy in ventricular aneurysm and ventricular tachycardia (3).

The contemporary definition of the f-QRS was defined by Das et al. (4) as the presence of an additional R wave (R') or notching in the nadir of the S wave, or the presence of more than one R' in two contiguous leads, corresponding to a major coronary artery territory on the resting 12-
lead ECG with filter range 0.16 - 100 Hz, AC filter 60 Hz, paper speed 25 mm/seconds and 10 mm/mV. Fragmentation of the wide complex QRS (BBB and paced rhythms) was defined by Das et al. (4) as various RSR’ patterns with or without a Q wave, with more than two R waves (R') or more than two notches in the R wave, or more than two notches in the down-stroke or upstroke of the S wave, in two contiguous leads corresponding to a major coronary artery territory. Although a positive response to CRT is consistently demonstrated over a wide range of clinical trials, the fact remains that only 60% - 70% of the patients respond to CRT and the condition of the others either remains unchanged or even deteriorates after CRT. It is also important to prescribe such an expensive therapy when a response is expected. Recently, the QRS width and bundle branch morphology emerge as important factors with regard to the response rate.

2. Objectives

The current study aimed to evaluate whether f-QRS is a predictor of response to CRT.

3. Patients and Methods

3.1. Patient Selection

Eighty patients who underwent CRT-D were retrospectively enrolled in this case control study and divided into two groups: subjects with f-QRS (the f-QRS group, n = 40) and those without f-QRS. They were followed up for a period of six months. The patients were enrolled in the study if they had a sinus rhythm, an LVEF of < 0.30, and prolonged intraventricular conduction with a QRS duration of > 130 milliseconds. All eligible subjects met guideline indications for the implantable cardioverter defibrillator (ICD) therapy.

Comparisons were made either within each group or between the two groups before and after CRT-D implantation in terms of the functional class, quality of life, reduction of the tachyarrhythmia events, mortality and echocardiographic findings (LVEF, left ventricular end diastolic dimension (LVEDD) and left ventricular end systolic dimension (LVESD). The episodes of hospitalization were also registered in both groups. The demographic data and past medical history of the patients were obtained from the outpatient clinic and medical data sheet records archived in the center. Intrinsic patients’ ECG was recorded. The ECGs of all patients were analyzed for the presence of f-QRS and pathologic Q waves in two or more anatomically contiguous leads by two independent cardiologists. The criteria used for f-QRS was derived from Das et al. (4).

3.2. Outcome Measures

3.2.1. Remodeling Effects

An echocardiographic response was defined as a reduction in LVEF and LVEDD and mitral regurgitation (MR) severity and an increase in LVEF after CRT implantation.

3.3. Clinical Response

The primary end point for clinical response was defined as a first HF event or death, whichever came first, during the follow-up. The secondary end point was defined as the advancement of the New York heart association (NYHA) class more than I during the follow-up. Cardiac mortality was also assessed as a secondary end point.

The study protocol was approved by the institutional review board and the subjects gave written informed consent for their participation in the study.

3.4. Statistical Analysis

All the statistical analyses were conducted using the SPSS ver.17 (SPSS Inc. Chicago, Ill). The mean and standard deviation of the qualitative variables were determined. Differences between the two groups were analyzed via the student t-test and with log transformation for continuous and the chi-square test for categorical variables. One-sample Kolmogorov test was used to evaluate the normal distribution of the two groups. P values < 0.05 (two tailed) were considered significant.

4. Results

Eighty patients were evaluated in this study [(40 with non-fragmented QRS and 40 with fragmented QRS), 55 (68.8%) male; mean age: 62.05 ± 11.25 years; 50 patients with ischemic and 30 with non-ischemic cardiomyopathy]. Baseline LV echocardiography indices are depicted in Figures 1, 2, and 3. Twelve patients (15%) had mild LV enlargement of whom eight had f-QRS. Sixteen cases (20%) had moderate LV dysfunction of whom seven had f-QRS. Fifty patients (62.5%) had severe LV enlargement of whom 23 had f-QRS. Two cases had a normal LV size and both had f-QRS. During the follow-up, an improvement was observed in echocardiographic parameters in both groups although patients without f-QRS showed more improvement (P = 0.02).

The patients’ symptoms reduced, and the MR severity (Table 2) improved in both groups when compared to their previous values before implantation (0.003), although the
difference between the two groups was not statistically significant (P = 0.3). This result could be significant in the clinical setting.

### Table 2. Severity of Mitral Regurgitation Among Patients Pre and Post Cardiac Resynchronization Therapy Implantation

<table>
<thead>
<tr>
<th>MR Severity</th>
<th>Pre-CRT Implantation</th>
<th>Post-CRT Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients</td>
<td>Number of Patients</td>
</tr>
<tr>
<td>Mild</td>
<td>36 (45)</td>
<td>41 (51)</td>
</tr>
<tr>
<td>Moderate</td>
<td>27 (34)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>Moderately</td>
<td>9 (10)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Severe</td>
<td>8 (10)</td>
<td>5 (6)</td>
</tr>
</tbody>
</table>

*Values’ unit is %.

In the present study, among all the patients (eighty), one case of ventricular tachyarrhythmia (VT) occurred that was treated with ICD shock, and two cases of hospitalization due to worsening of the heart failure symptoms were observed in f-QRS, although the difference was not statistically significant.

### 5. Discussion

The correlation between f-QRS and ischemic and non-ischemic cardiomyopathy with reduced LV function is investigated in some studies which reported that F-QRS was present in 23% - 75% of the patients with dilated cardiomyopathy (DCM) and narrow QRS complexes and it was common in patients with ischemic cardiomyopathy (5, 6). F-QRS is associated with intraventricular dyssynchrony in patients with non-ischemic DCM and would be useful to identify the patients who benefit from cardiac resynchronization therapy (1-3, 7, 8).

A wide QRS complex is observed in 14% - 47% of patients with heart failure. A wide QRS complex, especially left BBB, is associated with more advanced myocardial injury, a worse left ventricular function, and higher mortality than a narrow QRS complex (9).

Two studies showed that f-QRS and a wide QRS complex were associated with a worse prognosis in patients with DCM (1, 3). In patients with non-ischemic DCM (EF ≤ 40%), f-QRS is introduced as a strong predictor of mortality and arrhythmic events, and event-free survival in patients with f-QRS or a wide QRS complex (3). F-QRS is an independent predictor of lethal arrhythmic events (HR: 7.62) (ICD shock or antitachycardia pacing) in patients with ischemic or non-ischemic DCM who receive an ICD for primary or secondary prevention, but it could not predict death in the population (1). If the subjects are limited to DCM patients (both ischemic and non-ischemic) implanted by an ICD for...
primary prevention, the usefulness of f-QRS to predict arrhythmic events might be lost. Two studies showed that f-QRS was not associated with a higher risk of both arrhythmic events and mortality in patients with an ICD for primary prevention (2).

Despite the wide availability of clinical and investigational imaging modalities to evaluate the patient response to CRT with variable accuracy, a simple 12-lead remains the standard test to select the patients. Several ECG parameters are used to predict the response to CRT, including the baseline rhythm, QRS duration, QRS morphology, LV activation sequence, and PR interval. Prior studies failed to demonstrate improved response rates to CRT when adding echocardiographic measures of dyssynchrony, thus the QRS width is currently the sole criterion for treatment in eligible patients; considering the non-uniform effect of this technology in implanted patients, f-QRS might represent an underlying arrhythmogenic substrate. The distortion and fragmentation of the QRS occurs when normally smooth myocardial activation is disrupted (10). The cause of the disruption may be either structural or functional changes. In patients with coronary artery disease, f-QRS is a better marker of prior myocardial infarction than Q waves (4).

Myocardial scar and conduction disturbance result in dyssynchrony in the left ventricular systolic function. Fragmented QRS is associated with intra-ventricular systolic dyssynchrony in patients with a narrow QRS (7, 8). The patients with f-QRS might benefit from cardiac resynchronization therapy.

The present study identified one simple baseline electrocardiographic parameter that was associated with a favorable reverse remodeling effect in CRT patients.

A strong association was observed between the f-QRS and response to CRT in terms of reverse remodeling. No difference was noticed between the patients with an ischemic etiology of heart failure and patients with nonischemic cardiomyopathy. Independent of the patient characteristics, the presence of f-QRS was associated with a better response to CRT.

5.1. Conclusions

The prediction of the CRT response is complex and was the subject of extensive research over the past decade. Despite all known about CRT, a significant proportion of heart failure patients do not respond to CRT. However, careful analysis of simple ECG can yield impressive data which is difficult to replace with any of the available more sophisticated clinical tools. The current study demonstrated that f-QRS detected by the standard 12-lead ECG was a prognostic marker for response to CRT regardless of the etiology of heart failure. Large clinical trials are required to further evaluate the role of f-QRS to select patients for CRT implantation.

5.2. Study Limitations

The current study provided a nonrandomized retrospective analysis of a relatively small number of patients. An improvement was observed in the LV size in both groups, although no significant relationship was found. Comparison of MR between the two groups showed recovery after CRT implantation to appear in clinics but no significant relationship was detected. A significant difference was observed in LVEF, LVESD and LVEDD between the two groups. The results of the study showed that lack of f-QRS on ECG could predict an improved response, more reduction in LVED and LVESD, and more increase in EF in the patients after CRT-D implantation. The clinical characteristics and functional ability improved significantly in both groups and most of the patients who had NYHA class II after CRT implantation had f-QRS on ECG although no significant relationship was found in the NYHA class between the two groups. The presence of f-QRS in patients with heart failure could confirm a weaker response to CRT implantation according to echocardiography findings and could be considered as an accurate patient selection guide.

Footnote

Authors’ Contribution: Reza Mollazadeh, Samaneh Noori, Payman Tabatabaei, Zahra Emanjoo, and Masoud Eslami contributed in different parts of idea presentation, data gathering, writing, and submitting of the article.

References


