The role of the fragmented QRS complexes on a routine 12-lead ECG in predicting non-responsiveness to cardiac resynchronization therapy

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Abstract

Objective: Cardiac resynchronization therapy (CRT) is introduced as a promising therapeutic option in heart failure (HF) patients with ventricular dyssynchrony.The challenge, however, is identifying the patients who are suitable candidates for this procedure. Fragmented QRS (fQRS) is associated with subendocardial fibrosis and myocardial scars. In this study, we aimed to evaluate the role of fragmented QRS complex on a routine 12-lead ECG as a predictor of response to CRT.

Methods: Sixty-five consecutive patients with HF who underwent CRT, were studied. Patients' resting 12-lead ECGs were analyzed to find presence of fQRS by a cardiologist. Echocardiographic response to CRT was defined as ≥15% decrease in left ventricular end-systolic volume (LVESV) after CRT implantation. Response to CRT was compared between patients with and without fQRS.

Results: The study group included 27 women (41.5%) and 38 men (58.5%) with a mean (±SD) age of 62±12 years. 27 patients (41.5%) had fQRS in their basal ECGs. Totally 46 patients (70.8%) responded to CRT in a way that the mean left ventricular ejection fraction (%) significantly increased, and left ventricular end diastolic volume (LVEDV) significantly decreased after CRT ($p<0.001$ and $p=0.001$ respectively). In multivariate logistic analysis, lack of fQRS was found to be a predictor of response to CRT (OR: 4.553, 95% CI: 1.345-15.418, $p=0.015$).

Conclusion: We showed that the fQRS complex, as a sign of myocardial scar, predicts non-responsiveness to CRT. Therefore, fQRS may help selecting of CRT candidates. *(Anatol J Cardiol 2015; 15: 204-8)*

Keywords: cardiac resynchronization therapy, fragmented QRS, heart failure, systolic volume

Introduction

Heart failure (HF) is a single cardiovascular disease with increasing incidence and prevalence, which is associated with poor quality of life and high mortality rate. It is the first cause of hospitalization in medical patients, and has affected more than a million elderly adults in the United States (1, 2). Cardiovascular disease, especially HF is prevalent in Middle-East with an increasing incidence of almost 3500 people per one hundred thousand (3, 4).

Left ventricular (LV) dyssynchrony is frequently occurring in HF patients, especially in those with wide QRS intervals (5). Recently, cardiac resynchronization therapy (CRT) is emerged as a useful management strategy for patients with wide QRS intervals, and for symptomatic HF who are on maximal medical therapy.

Some research have shown that CRT using biventricular pacing can be a promising technique with benefits in patients with New York Heart Association (NYHA) class III or above, and widened QRS (6-8). The proposed mechanisms for benefits of CRT on HF patients are optimization of the AV-delay resulting in synchrony, in ventricular contraction and an improvement in systolic function and mitral regurgitation (MR) (9).

Despite these impressive results, almost 30% of patients failed to show improvement in clinical symptoms, and 40-50% of patients had no improvement in LV function on echocardiography (10-13). It is suggested that insufficient evidence of mechanical dyssynchrony before device implantation might be one of the major reasons, while others include the presence of transmural scar at posterolateral wall, lack of myocardial contractile reserve, severe MR, suboptimal LV lead position, and inappropriate device programming (4).

LV mechanical dyssynchrony is characterized by the differences in the timing of contraction between different myocardial segments, which is commonly observed in patients with conges-

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tive HF. Its presence varies by not only the methods of assessment, but also by characteristics of the study population including the QRS duration, loading condition, severity of coronary artery disease, LV hypertrophy, and LV remodeling. Therefore, the ECG criteria of QRS width ≥120 ms adopted in the current guidelines may not be the optimal tool in identifying the patients who benefit most from CRT or defining the presence of mechanical dyssynchrony (14, 15).

The myocardial scar causes heterogeneous ventricular activity, and is associated with alteration in QRS morphology, leading to terminal conduction delay or a fragmentation of the QRS complexes on 12-lead ECG (16). Fragmented QRS (fQRS) includes various RSR' patterns with different morphologies of the QRS complexes with or without the Q wave on a resting 12-lead ECG (17). fQRS is associated with subendocardial fibrosis and myocardial scars (17, 18) and it has been shown that response to CRT is associated with the extent of myocardial scar tissue in patients with ventricular dyssynchrony (19, 20).

Since the response to CRT varies significantly among individuals, and a large number of patients do not respond to this expensive therapeutic method,it is important to find the predictors responsiveness before the procedure begins.

Different studies have previously focused on mechanical dyssynchrony, interventricular mechanical delay (21) and QRS duration (22) in HF patients candidate for CRT, but few studies have been performed to assess the role of the fQRS complexes in predicting non-responsiveness to CRT. Çelikyurt et al. (23) evaluated relationship between fragmented QRS and response to CRT and their findings were very interesting and they suggested further studies to confirm the findings. On the other hand, Rickard (24) reported fQRS is not a predictor of progressive ventricular remodeling in HF patients undergoing CRT. Accordingly, the aim of this study was to evaluate the role of the fQRS complexe on a routine 12-lead ECG in predicting non-responsiveness to CRT in HF patients.

Methods

Patients' population

In this cross-sectional study, 65 consecutive patients with HF who were scheduled for CRT at our university hospital, from september 2011 to september 2012, were enrolled. The inclusion criteria were drug-refractory NYHA class III or IV HF, depressed left ventricular ejection fraction (LVEF) ≤35%, and prolonged QRS duration (≥120 ms). Patients were excluded if they were right bundle branch block, non-sinus rhythms, or had CRT insertion within the last 3 months. The etiology of HF was considered ischemic in the presence of significant coronary artery disease (more than fifthy percent stenosis in at least one of the major coronary arteries) and/or previous revascularization or a history of myocardial infarction. All patients were on angiotensin converting enzyme or angiotensin receptor blocker, beta-blockers and low dose of spironolactone before and after CRT implantation; if the patients were symptomatic, diuretic was added to medication.

The study protocol was accepted by our local Ethical Committee. Written informed consent was obtained from all patients.

Study protocol

Electrocardiography

Patients' resting 12-lead ECGs (0.5 Hz to 150 Hz, 25 mm/s, 10 mm/mV) were analyzed for fQRS complexes by an expert electrophysiologist who was blinded to the aims of the study and the results of the CRT. In wide-complexes QRS, fQRS was defined by the presence of >2 notches on the R wave or the S wave and had to be present in ≥2 contiguous corresponding to a major myocardial segment (Fig. 1) (17). The presence of fQRS in two or more contiguous anterior leads (V_1 to V_5), two or more lateral leads (I, aVL and V_6), and in two or more inferior leads (II, III and aVF), and the presence of fQRS in V_1 and V_2 corresponded to the posterior myocardial segments were recorded.

CRT device implantation

CRT device implantations were performed by electrophysiologists. Right atrial and right ventricular leads were implanted using a transvenous approach. LV leads were inserted by a transvenous approach through the coronary sinus into a cardiac vein in the majority of patients. In two patients, when the transvenous lead failed to be placed due to procedural difficulty, a minimally invasive epicardial lead was placed by a cardiothoracic surgeon.

LV lead location

Electrophysiologists performed a pre-implantation coronary venous angiogram in at least 2 orthogonal views (left anterior oblique and right anterior oblique, 20° to 40°), stored post implantation fluoroscopic images in the same views, and obtained post procedural chest x-rays (anteroposterior and lateral views) before the patients was discharged. A detailed evaluation of the pre-implantation venogram and post implantation LV lead images was made to locate the final position of the LV lead.

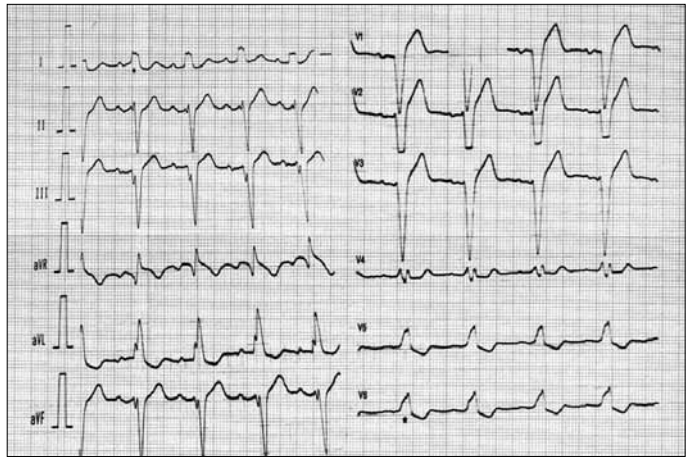

Figure 1. Electrocardiography showing fragmented QRS complex

Table 1. The characteristics of patients with fQRS and non fQRS

Characteristic	fQRS (n=27)	Non-fQRS (n=38)	*P*
Age, years	62.8±13.4	60.8±11.9	0.53
Male/female	16/11	22/16	0.91
QRS duration, ms	142.6±13.5	137.4±11.8	0.10
LVESV, mL	173.5±80.6	155.9±58.5	0.34
LVEDV, mL	212.9±82.3	195.9±65.9	0.89
LVEF, %	17.6±6.5	19.8±6.3	0.18

fQRS - fragmented QRS; non-fQRS - non-fragmented QRS; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESV - left ventricular end-systolic volume

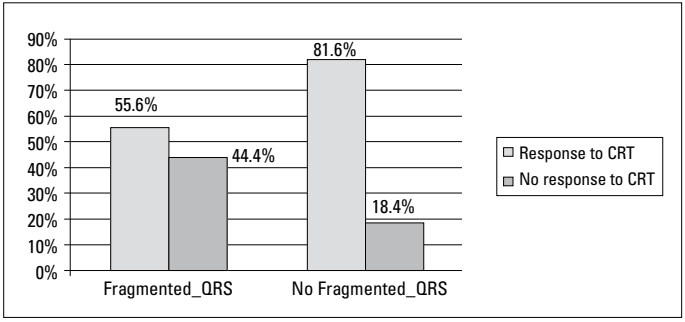

Figure 2. Response to CRT in fQRS and non fQRS groups

Echocardiography

All patients underwent transthoracic echocardiography (VIVID S6; General Electronic Company, Wauwatosa, WI, USA) by cardiologists who were blinded to the current study before and 3-6 month after the CRT implantation. Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were recorded, and LVEF was calculated from the conventional apical two- and four-chamber images using the biplane Simpson's technique. All the echocardiographic measurements after CRT implantation were made with the device in active pacing mode. The response to CRT was defined as ≥15% decrease in LVESV at follow-up.

Statistical analysis

Data were analyzed using a statistical software program (SPSS version 18.0; SPSS Inc, USA). Continues data were presented as mean±SD and were tested for normal distribution via the Kolmogorov-Smirnov (K-S) test. A comparison between clinical and echocardiographic variables before and after CRT was performed by paired sample t test. Categorical variables were compared by the chi-square test. Multivariate logistic regression analysis in backward- LR method was used for identifying variables to be predictive of the response to CRT. The sensitivity, specificity, positive predictive value and negative predictive value were calculated. A p value <0.05 was considered significant.

Results

Sixty-five patients met the inclusion criteria, included 27 women (41.5%) and 38 men (58.5%) with a mean (±SD) age of 62±12 years, while the maximum age of the participants was 82 years, and the minimum age was 24 years. Patients were categorized into two subgroups according to presence (n=27; 41.5%) or absence (n=38; 58.5%) fQRS complexes in their basal ECGs. Demographic, electrocardiographic and echocardiographic characteristics of the study population in relation with the existence of fQRS complex are shown in Table 1.

Totally, among 65 HF patients, 46 patients (70.8%) responded to CRT and 19 patients (29.2%) were non-responders in a way that the mean LVEF (%) significantly increased and LVESV and LVEDV decreased significantly after CRT in responders (p<0.001, p<0.001 and p=0.001 respectively). Table 2 shows patient's echocardiographic responses to CRT in association with the existence of fQRS in their ECGs.

The response to CRT was defined as ≥15% decrease in LVESV after CRT, and was compared according to some variables such as patients' gender, the region of LV lead insertion (anterolateral, posterolateral, lateral, and posterior) and the existence of fQRS. There were no association between patients' gender, or the region of LV lead insertion with their response to CRT (p=0.6, p=0.17 respectively).

In logistic regression analysis, significant associates of response to CRT were evaluated adjusting for sex, QRS width, lead position, and fQRS. Existence of fQRS was associated significantly with a poor response to CRT (OR: 4.553, 95% CI, 1.345-15.418, p=0.015). The sensitivity, specificity, positive predictive value and negative predictive value of fQRS in predicting echocardiographic non-responsiveness to CRT were 91.3%, 47.3%, 80.7% and 69.2% respectively. Figure 2 shows the distribution of responsiveness and non-responsiveness to CRT according to presense and absence of fQRS complex.

In all patients (65 HF patients) and in a subgroup analysis of patients with ischemic HF (n=59 patients; 91%), fQRS significantly was associated with non-responsiveness to CRT. Due to the small number of non-ischemic HF (n=6 patients; 9%), evaluation in this subgroup was not possible. Therefore, the results presented are based on all patients.

Discussion

CRT is considered as an important non-pharmacological treatment option for patients with wide-QRS and advanced CHF, who are on optimal medical treatment. Several investigations in this field have demonstrated significant improvements in NYHA class, quality of life score, and LV function following CRT (7, 25-28). Our study also supported the positive effect of CRT in LV function in HF patients. CRT resulted in the optimization of the atrio-ventricular (AV) by AV-delay interval programming, shortened the interventricular conduction delay, resulting in a reduction of the RV-LV dyssynchrony and reversed the intraventricular conduction delay, which is mainly caused by mechanical dispersion of the motion between the septum and the lateral wall. So A-V optimization and the restoration of inter- and intraventricular synchrony all contribute to the beneficial effects of CRT such

Table 2. Comparison of the echocardiographic indexes before and after CRT in patients with and without fQRS complex

	fQRS (n= 27)			Non-fQRS (n= 38)			Total (n= 65)		
	Before CRT	After CRT	*P*		After CRT	*P*	Before CRT	After CRT	*P*
LVESV, mL	173.5±80.6	158.4±74.9	0.108	155.9±58.5	132.8±49.9	<0.001	163.2±68.5	143.4±62.3	<0.001
LVEDV, mL	212.9±82.3	200.9±80.1	0.177	195.9±65.9	174.7±53.5	<0.001	202.9±73.1	185.6±66.6	0.001
LVEF, %	17.6±6.5	22.3±4.8	0.002	19.8±6.3	24.5±9.5	0.001	18.8±6.4	23.6±9.2	<0.001

CRT - cardiac resynchronization therapy; fQRS - fragmented QRS; LVEDV - left ventricular end-diastolic volume; LVEF - left ventricular ejection fraction; LVESV - left ventricular end-systolic volume; non fQRS- non fragmented QRS

as improvement of systolic function, reduction of mitral regurgitation and reverse remodeling (29).

The current recommendation for CRT is based on the QRS duration. Although patients are selected according to current patient selection criteria, an important proportion of them do not respond to CRT (23, 30). However, results of many CRT studies indicates that 30-40% of the patients failed to respond to CRT (13). The 29% non-responders in our study were in agreement with previous studies. Therefore, additional selection criteria for CRT are needed to increase the likelihood of response. Despite the intense research focus this topic is garnered, accurately predicting non-responsiveness and poor long-term outcomes in HF patients undergoing CRT is still remained a challenge. Based on the definition of fQRS by Das et al. (17), in the patients with wide QRS duration, fQRS had a sensitivity and specificity for myocardial scar of 86.8% and 92.5%, respectively. Similar studies in patients undergoing nuclear stress test revealed that fQRS is associated with old scars (16, 31). Based on this finding, we sought to determine whether fQRS was associated with progressive remodeling or not, indicating poor response to CRT.

The results of our study showed that the lack of fQRS was a predictor of the response to CRT,in a way that the odds ratio for non-responsiveness to CRT in fQRS relative to non-fQRS was 4.553 (OR: 4.553, 95% CI, 1.345-15.418, p=0.015). This is similar to the study by Çelikyurt et al. (23) which showed reverse remodeling after 6 months follow-up was significantly more common in patients with non-fragmented wide-QRS (35% vs. 89%, p=0.001). However in a study by Rickard et al. (24) they found no difference in indices of LV remodeling or rates of all-cause mortality between patients with and without fQRS. Reasons they mentioned in their study for the patients with fQRS were more likely being female gender, having higher incidences of left bundle branch block, lower incidences of right bundle branch block and non-specific intraventricular conduction delay, and wider baseline QRS duration in compare to those without fQRS. In the recently published large MADIT-CRT study, female gender, wider baseline QRS duration, and the presence of a left bundle branch block were associated with improved outcomes following CRT (32). Therefore, these factors, especially wide baseline QRS duration, which portend favorable outcomes, may overcome the negative influence that fQRS may have. As we see in Table 1 in our study similar to Çelikyurt et al. (23) study, there was no significant difference between patients gender and baseline mean QRS duration in fQRS and non fQRS group. Our study showed; sensitivity, specificity, positive predictive value and negative predictive value of fQRS in predicting non-responsiveness to CRT were 91.3%, 47.3%, 80.7% and 69.2%, respectively.

The existence of leads with fQRS in our non-responder patients may relate to reduced LVEF, the presence of more progressive diseases and extensive scar tissues. Our data suggested that there are other factors such as fQRS besides the mechanical dyssynchrony which may provide useful information for predicting the response to CRT. Presence of fragmentation in patients with wide-QRS may help identifying patients who do not response to CRT.

Study limitations

Our study had several limitations; such as non-randomized design, the small study sample and the patients enrolled from a single care center. This study did not include an assessment of myocardial scar, which would have been useful to determine the relationship between fQRS and scar in this population.

Conclusion

We showed the fragmentations of QRS complex as a sign of myocardial scar predicted non-responsiveness to CRT, which may help in selecting the CRT candidates.

Conflict of interest: None declared.

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