ORIGINAL ARTICLE

DIAGNOSTIC ACCURACY OF NUMBER OF FRAGMENTED QRS LEADS IN PREDICTION OF CARDIAC RESYNCHRONIZATION THERAPY RESPONSE IN PATIENTS WITH HEART FAILURE

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Objectives: We investigated the diagnostic accuracy of fragmented QRS (fQRS) numbers in surface electrocardiogram (ECG) in heart failure (HF) patients for prediction of cardiac resynchronization therapy (CRT) non-responders.

Methodology: In this study, patients with HF who were candidates for CRT implantation were enrolled. A 12-lead surface electrocardiogram was conducted with the aim of finding fQRS. Presence of more than 2 notching in the R or S wave in wide QRS complexes in at least two adjacent leads corresponding to a coronary bed, considered as fQRS. All patients underwent transthoracic echocardiography 3-6 months after the CRT implantation for the evaluation of Left Ventricular End Diastolic Volume (LVEDV), Left Ventricular End Systolic Volume (LVESV), and Left ventricle ejection fraction (LVEF). The data were analyzed by SPSS v.22 software. P-value of less than 0.05 considered significant.

Results: We investigated on a total of 73 patients with HF that 64.38% of them responded to CRT. Most of responders were patients without fQRS complexes (80%). LVEF, LVESV, and LVEDV were different significantly before and after CRT implantation in patients with fQRS ($p<0.001$). Our results showed that the presence of at least one fQRS can lead to non-responsiveness to CRT. Therefore, we take cut-off point equal-greater than one into account as the best cut-off point for response to CRT. The area under the curve (AUC) for CRT prediction was 0.715 (95% CI: 0.598-0.815, P=0.003).

Conclusion: In conclusion, the presence of even one fQRS in the surface ECG can predict CRT non-responsiveness with good accuracy.

Keywords: Heart Failure, Cardiac Resynchronization Therapy, Electrocardiography, QRS complex, fQRS

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INTRODUCTION

Heart failure (HF) is a worldwide health problem and its current prevalence is 64.34 million cases (8.52 per 1,000 inhabitants) all around the world which forced billion dollars of expenditure on health-care systems.[1]

Several conduction abnormalities that alter the timing and pattern of ventricular filling and ventricular contraction are seen in chronic heart failure. These altered patterns called ventricular dyssynchrony, defined by prolonged QRS (>120ms), is common in one-third of heart failure patients. Cardiac resynchronization therapy (CRT), by pacing the right and left ventricle simultaneously, is one of the proven treatment options for these patients. It is often used in treatment of symptomatic HF patients (NYHA II, III and ambulatory IV) with left ventricular (LV) function equal or less than 35% and a widened QRS complex[2,3] mostly in patients with left bundle branch block (LBBB).[4] Many studies showed that CRT can improve the symptoms and clinical outcomes of patients with HF.[5,6] However based on the current ACC/AHA guideline criteria for CRT candidates, some patients are still non-responders.[7]

ECG abnormalities represent cardiac pathologies[8] such as ischemic and non-ischemic cardiac myopathy.[9] Therefore, ECG was considered as one of the available modalities for diagnosis non-responders in different studies.[9-11]

Among the abnormalities, Fragmented QRS (fQRS) is a convenient marker of myocardial scar with a higher sensitivity and negative predictive value compared with the Q wave.[12] It is defined by various RSR'-like deviations with different morphologies in two contiguous leads related to coronary territory in 12 lead ECG.[12,13] As an indicator of myocardial scar, fQRS could be a predictor of CRT non-responder patients with ventricular dyssynchrony and it can be useful selecting CRT candidates.[6]

In the light of foregoing, CRT is a valuable treatment in HF patients. As the number of fragmented QRS is a new index in ECG which can help us detecting CRT candidates more accurately, the aim of this study was to evaluate the diagnostic accuracy of fQRS numbers in surface ECG in HF patients which leads to predicting non-responders to CRT.

METHODOLOGY

Study population: In this cross-sectional study, patients with HF who were candidates for CRT implantation in our heart center were enrolled. Inclusion criteria included patients in sinus rhythm with grade III or IV of NYHA class who were refractory to drug therapy, patients with LVEF less than or equal to 35%, and QRS with left bundle branch block (LBBB) morphology greater than or equal to 120 ms.

Exclusion criteria was the presence of right bundle branch block (RBBB), no atrial fibrillation (AF) rhythm in the ECG, or patients who had CRT implantation for the past 3 months. All patients treated with Angiotensin Converting Enzyme or Angiotensin Receptor Blocker, B blockers and low dose spironolactone before and after CRT implantation; Diuretics were also added to their treatment if patients were symptomatic.

The study protocol was approved by the ethics committee of our university (Research project number: 93072219) and conformed to the standards of the Declaration of Helsinki of 1975. All persons gave their informed consent prior to their inclusion in the study.

Electrocardiography: During the study, with the aim of finding fQRS, a 12-lead surface electrocardiogram of patients was evaluated by an electrophysiologist. Presence of more than 2 notching in the R or S wave in wide QRS complexes in at least two adjacent leads corresponding to a coronary bed, considered as fragmented QRS. The adjacent leads were evaluated in three categories: anterior (V1 to V5), lateral (I, aVL, V6) and inferior (II, III, aVF) (Figure 1).

CRT device implantation: CRT implantation was performed by an electrophysiologist. The right atrium and ventricular leads were implanted through the Transvenus Approach. Implantation of the left ventricular lead was done through the cardiac vein via the coronary sinus by the same approach. Two orthogonal view via Venogram were taken before embedding the left ventricular lead, and 2 fluoroscopic images from the same view were taken after the implantation. After the completion of procedure Chest X-Ray (anteroposterior and lateral) was also taken from the patient to determine the final location of the lead in the ventricle.

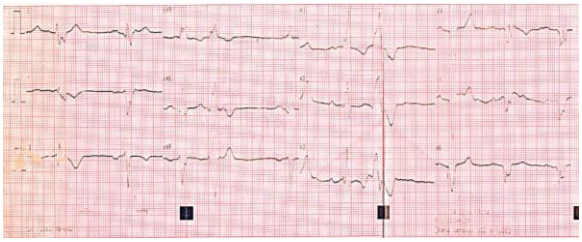

Figure 1: An example of fQRS

Echocardiography: All patients underwent transthoracic echocardiography by an echocardiologist 3-6 months after the implantation of CRT. Left Ventricular End Diastolic Volume (LVEDV), Left Ventricular End Systolic Volume (LVESV) and Left ventricle ejection fraction (LVEF) were evaluated. The response to CRT was considered as improvement in NYHA functional class (at least one class) and reduction in LVESV ≥15% and/or absolute increased in LVEF ≥10%.

Statistical analysis: Based on CRT response, patients were divided into two groups of CRT responders and non-responders. The data were analyzed by SPSS v.22 software. Continuous data were reported as mean and standard deviation after checking their distribution by Kolmogorov-Smirnov (KS) test. Comparison of these data was performed using independent t-test.

In our study, we used the Mann Whitney test due to absence of normal distribution in Kolmogorov-Smirnov test in both CRT responders and non-responders groups. For discrete data which was reported as frequency and percentage, Chi-Square test was used.

P value of less than 0.05 considered significant. The ROC Curve analysis was also used to determine the cut off value for the number of Fragmented leads to predict CRT response.

RESULTS

We studied a total of 73 patients with HF with mean age of 61.9 ± 12 years old (24-82 years old) that 44 (60.27 %) of them were men.

Evaluation of CRT response as the main variable of this study showed that out of 73 patients, 47 of subjects (64.38%) responded to CRT.

Table 1 illustrated the comparison of CRT response in both groups of with and without fragmented QRS on the surface electrocardiogram. As the tables shows there is a significant difference between two groups. (p<0.001).

Table 1: Comparison the number of CRT response in both with and without fragmented QRS groups

Groups	N (%)	Responders	Non-responders
With fQRS	18 (24.66 %)	3 (16.67 %)	15 (83.33 %)
Withou t fQRS	55 (75.34 %)	44 (80 %)	11 (20 %)

Table 2 represents the results of comparing quantitative factors (LVEF, LVESV, and LVEDV) before and after CRT implantation in patients with fragmented leads. As the table shows, there was a significant difference before and after CRT implantation.

According to the table 3, as the number of fQRS increases, the sensitivity and specificity increases and decreases, respectively. According to the aforementioned standard definition, the existence of 2 fQRS complexes in at least two adjacent leads is necessary.

Table 2: Comparison of LVEF, LVESV, and LVEDV before and after CRT implantation in patients with fragmented Leads

Variable	Before CRT implantation	After CRT implantation	P-value
LVEF	20.56 ±7.85	23.17±10.66	0.001
LVESV	147.39±82.20	155.44±80.10	<0.0001
LVEDV	180.89±86.87	189.06±84.81	<0.0001

However, our results showed that the presence of at least one fQRS can lead to non-responsiveness to CRT. Therefore, we take cut-off point equal-greater than one into account as the best cut-off point for response to CRT. The area under the curve (AUC) for CRT prediction was 0.715 (95% CI: 0.598-0.815, p=0.003) (Figure 2).

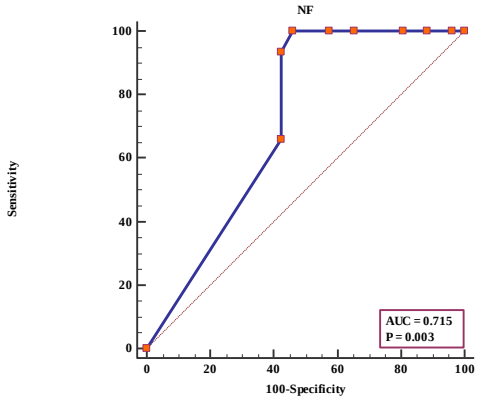

Figure 2: The AUC for CRT prediction

Table 3: Number of fragmented QRS and their sensitivity and specificity

Number of Fragmented	Sensitivity	95% CI	Specificity	95% CI	Positive Predictive Value	Negative Predictive Value
0	65.96	50.7 - 79.1	57.69	36.9 - 76.6	73.80%	48.40%
Equal less than 1	93.62	82.5 - 98.7	57.69	36.9 - 76.6	80%	83.30%
Equal less than 2	100	92.5 - 100.0	53.85	33.4 - 73.4	79.70%	100%
Equal less than 3	100	92.5 - 100.0	42.31	23.4 - 63.1	79.70%	100%
Equal less than 4	100	92.5 - 100.0	34.62	17.2 - 55.7	73.40%	100%
Equal less than 5	100	92.5 - 100.0	19.23	6.6 - 39.4	69.10%	100%
Equal less than 6	100	92.5 - 100.0	11.54	2.4 - 30.2	67.10%	100%
Equal less than 7	100	92.5 - 100.0	3.85	0.10 - 19.6	65.30%	100%
Equal less than 8	100	92.5 - 100.0	0	0.0 - 13.2	64.40%	-

DISCUSSION

In this study, we evaluated 73 patients with HF who were candidates for CRT implantation in our heart center.

The assessment of fQRS in the surface ECG provides a noninvasive preimplantation parameter to predict response to CRT. We investigated on the minimum number of fQRS which can cause CRT non-responsiveness. Our results showed that even a minimum number of fQRS can lead to non-response to CRT.

CRT devices decrease the RV-LV dyssynchrony that mainly caused by mechanical scattering of motions between the septum and the lateral wall. Therefore, intraventricular synchrony can lead to beneficial effects such as improved systolic function, reduced mitral regurgitation, and reverse remodeling. Despite all these effects, a significant percentage of patients are selected based on current guideline criteria, which are based on the width of the QRS, do not respond to this treatment.[6,9] Therefore, criteria which increase the likelihood of CRT response is important to be considered.

Lack of proper muscle tissue with contractile properties and their replacement with fibrotic or scar tissue (in the context of ischemic or non-ischemic causes) is one of the important causes of inadequate response. ECG is one of the affordable and inexpensive methods can be used to prove scar tissue in the heart. Fragmentation in the QRS complex is a sign of scar tissue in the myocardium.[12,14] According to a study by Das et al, wide complex QRS with fragmentation had a sensitivity and specificity of 86.8% and 92.5%, respectively, for cardiac scar.[15] Similar studies in patients undergoing nuclear stress testing have shown that fQRS is associated with older scars.[16,17]

For that reason, several studies have been conducted to investigate the relation between fQRS and CRT response.

In our previous study which conducted on 65 patients with HF in whom CRT were implanted, the role of fQRS in the routine electrocardiogram of HF patients in predicting non-responsiveness to CRT was investigated. FQRS as a sign of myocardial scar was shown to be capable of predicting non-responders to CRT and may be helpful in selecting patients.[6]

In the study by Yang et al.[18] the correlation between reverse remodeling in cardiac geometry and electrical remodeling of fQRS after CRT implantation were investigated. According to the data of this study, a decrease of ≥1 fQRS after the implantation of CRT is reflecting a long-term electrical remodeling in the patient and is associated with favorable response.

In a cohort study which conducted by Dr. Celikyurt et al.[9] on 105 patients with HF who underwent CRT to investigate the association between fQRS lead numbers and CRT response, it was concluded that the greater need for cardiac revascularization, the higher probability of cardiac death, and all-cause mortality are associated with scar tissue burden. So the individuals with a higher average number of fQRS leads were significantly associated with non-responder patients, and higher numbers of fQRS leads predicted non-responsiveness to CRT.

Another study by Celikyurt et al.[19] carried out in 2014. They investigated the association between resolution of fQRS and CRT response on 67 patients with LBBB and fQRS on their ECG who were candidates for CRT implantation. In their study after 6-months follow-up, patients whose fQRS were resolved, significantly responded to CRT more than the other patients (89% vs. 12%, P=0.001). Therefore, they reported that resolution of fQRS is related with CRT response.

Just as the higher average number of fragmented leads are effective in responding to CRT, knowing the minimum number of fragmented leads that can affect CRT is also important.

In finding the appropriate cutoff point for determining the minimum number of fragmented leads to predict failure to respond to CRT, the study data showed that the best Cut Off number of fragmented QRS is one with 93.62% sensitivity and 57.69 % specificity. Therefore, according to our findings, patients with a minimum number of equal-more than one fragmented QRS did not respond to CRT appropriately.

Limitation: Our study has two limitations. Firstly, it was a single-center study. Secondly, we investigated on the small number of patients due to its inclusion criteria. Therefore, further studies are needed to confirm our findings.

CONCLUSION

In conclusion, the presence of even one fQRS in the surface ECG can predict CRT non-responsiveness with good accuracy.

AUTHORS' CONTRIBUTION

MAA and AS: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. MAA, HM, AP, ZH, AS: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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