The Evaluation Of The Response To Cardiac Resynchronization Therapy In Patients With Dilated Cardiomyopathy By Using Fragmented QRS

Non-İskemik Dilate Kardiyomyopati Hastalarında Fragmante QRS'in Bi-ventrikuler Pacemaker Tedavisine Etkisi

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ABSTRACT

Introduction: Cardiac resynchronization therapy (CRT) is an effective treatment in heart failure however; identifying the suitable patients is difficult. Fragmented QRS (fQRS) complex is a myocardial conduction abnormality that indicates myocardial scar. This study was conducted to find out the response of non-ischemic dilated cardiomyopathy (NCMP) to CRT by using fQRS.

Methods: 56 patients were enrolled. 32 patients had fQRS (57.1%) and 24 had no fQRS (46.9%) on electrocardiography (ECG). All patients were suitable for CRT treatment. The two groups (fQRS and no fQRS) were evaluated before and after (1 year) CRT by using clinical status, ECG, and echocardiographic parameters. Continuous parameters were compared with Paired Samples T-test.

Results: During the follow-up period; comparison of QRS (p=0.46, p=0.61), and NYHA class (p=0.29, p=0.57) were not statistically significant before and after CRT, respectively (fQRS and no fQRS). In addition, the change in left ventricular ejection fraction is not statistically significant (p=0.12).

Conclusion: fQRS presence is not associated with CRT response in patients with NCMP.

Key words: Cardiac Resynchronization Therapy, Electrocardiography, Heart Failure, Fragmented QRS

ÖZET

Giriş: Kardiyak resenkronizasyon tedavisi (KRT) kalp yetmezliğinde etkili bir tedavidir ancak; uygun hastaları belirlemek zordur. Fragmente QRS (fQRS) kompleksi, miyokardial skarı gösteren iletim anormalliğidir. Bu çalışma, non-iskemik dilate kardiyomiyopatili (NKMP) hastalarda fQRS'in KRT yanıtına etkisini değerlendirmek için yapılmıştır

Yöntemler: Çalışmaya prospektif olarak 56 hasta alındı. Elektrokardiyografide (EKG) 32 hastada fQRS (%57.1) mevcuttu. KRT tedavisine uygun olmayan hastalar çalışma dışı bırakıldı. Klinik durum, EKG ve ekokardiyografik parametreler kullanılarak KRT öncesi ve sonrası (1 yıl) iki grup (fQRS ve fQRS yok) arasındaki farklılık değerlendirildi. Sürekli parametreler Paired Samples T-testi ile karşılaştırıldı.

Bulgular: Takip döneminde; fQRS olan ve olmayan grup arasında QRS süresi (p=0.46, p=0.61) ve NYHA fonksiyonel sınıfı açısından (p=0.29, p=0.57) KRT öncesi ve sonrası istatistiksel olarak anlamlı değildi. Ayrıca sol ventrikül ejeksiyon fraksiyonundaki değişim açısından istatistiksel anlamlılık saptanmadı (p=0.12).

Sonuç: NKMP'li hastalarda fQRS varlığı KRT yanıtı ile ilişkili değildir.

Anahtar Kelimeler: Kardiyak Resenkronizasyon Tedavisi, Elektrokardiyografi, Kalp Yetmezliği, Fragmante QRS

INTRODUCTION

Cardiac resynchronization therapy (CRT) is considered an important treatment option in selected patients with heart failure (HF). It has been proven that CRT reduces HF symptoms and hospitalizations, improves exercise capacity, quality of life, and reduces mortality [1].

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However, about 30% of patients do not benefit from CRT, although they are selected according to appropriate patient selection criteria. It has been shown that the presence of left ventricular dyssynchrony is an important determinant of the response to the CRT [2-4]. The treatment of the patients with HF also creates a significant economic burden, and more than 50% of this burden is due to hospitalization. Efficacy criteria of HF related to long-term survival, morbidity, and quality of life of patients who have been followed up medically should be compared with patients who have been implanted CRT before [5]. In order to effectively use limited health resources, it should be identified the characteristics of the patient group that may benefit the most from CRT treatment and CRT implantation should be performed as a priority. It has been reported that the QRS fragmentation (fQRS), defined as the notching pattern in the QRS complex on a standard 12-lead ECG, is a marker of adverse cardiac events in patients [6]. The presence of fQRS in patients with non-ischemic dilated cardiomyopathy (NCMP) has been shown to be associated with late gadolinium enhancement in MRI that is related with myocardial scarring and increased ventricular arrhythmias [7]. Myocardial scarring shown by nuclear imaging and MRI has been found to be associated with progressive remodeling and poor outcomes in patients undergoing CRT implantation [8, 9]. In this study, we aimed to investigate the effect of fQRS on CRT response in CRT implanted patients that diagnosed with NCMP before.

METHODS

Study Population

This study consisted of 91 patients with advanced HF symptoms and wide QRS complexes with planned implantation of a CRT device. The study inclusion criteria were left ventricular ejection fraction (LVEF) ≤ 35%, severe HF symptoms despite optimal medical treatment [New York Heart Association (NYHA) Class II, III or ambulatory IV], QRS duration ≥ 130 msec, complete left or right bundle branch block morphology and sinus rhythm. Patients with atrial fibrillation (AF), wide QRS complexes with non-LBBB or non-RBBB patterns, ischemic heart failure, heart failure with QRS duration<130 msec were excluded from the study. Patient selection and exclusion criteria are presented in Figure 1.

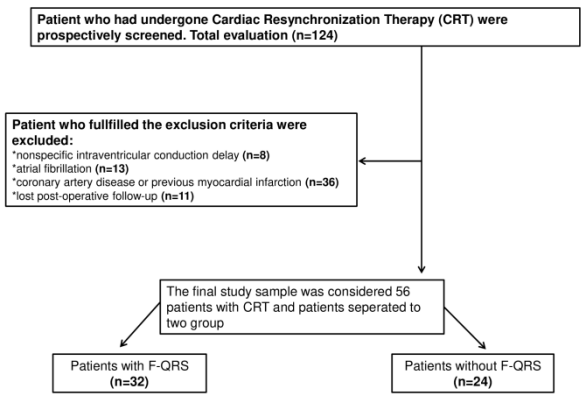

Figure 1. *Patient selection and exclusion criteria*

Optimal pharmacological treatment was applied to all patients before and after CRT implantation. All patients were followed up at the outpatient clinic every 3 months at regular intervals. The clinical conditions, NYHA functional capacities, electrocardiographic and echocardiographic parameters of the first-year follow-up were also analyzed. Informed consents about CRT implantation and data collection were taken from all patients. This study was carried out in accordance with the October 2008 Declaration of Helsinki and the study was approved by our local ethics committee (2016/3/4).

Electrocardiography

12 lead ECGs before and 1 year after the CRT implantation were recorded. All standard 12-lead ECGs were recorded by a standardized 25 mm/sec, 60 Hz (between 0.5 to 150 Hz), and 1 mV/cm ECG recorder (GE Marquette Medical Systems, Milwaukee, WI) at rest. ECG analyses were performed digitally using the MUSE (R) Cardiology Information System connected to

a personal computer (version 7.1.1.). A magnifying glass was used on the computer to minimize errors during measurement. ECG analyses were performed by two independent electrophysiologists who were blind to the study. The disagreement between 2 electrophysiologists was resolved by consensus.The fQRS was defined as various RSR′ patterns with or without a Q wave, with greater than two R waves (R′) or greater than two notches in the R wave, or greater than two notches in the downstroke or upstroke of the S wave, in two contiguous leads corresponding to a major coronary artery territory [10] (Figure 2). The QRS duration was measured from all the ECG leads between the beginning of the QRS complex and the end of the S wave (deceleration to the isoelectric line), and the longest QRS duration was selected.

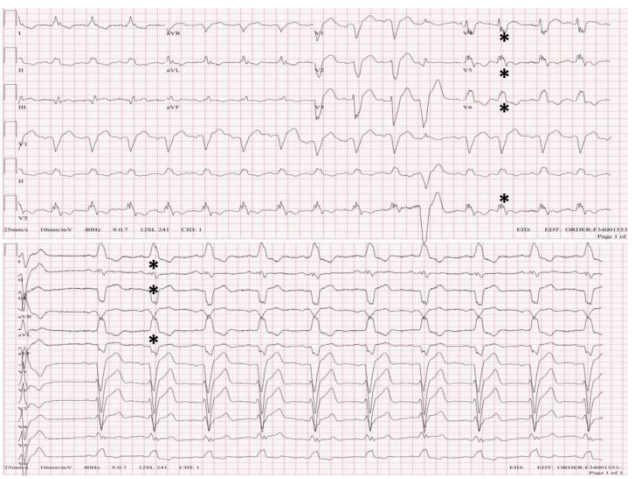

Figure 2. *Examples of Fragmanted QRS complexes of our study population.*
*Fragmented QRS complexes were shown as **

CRT Device Implantation:

All CRT device implantations were performed from the left infra-clavicular venous area. All of devices have defibrillator function. The left ventricular electrodes were all bipolar and implanted transvenously by an electrophysiologist targeting the lateral or postero-lateral coronary sinus veins. Patients who did not have a suitable venous branch for the left ventricular lead or who could not be performed the CRT implantation were excluded from the study. Pacing configuration that provides the optimal QRS narrowing was applied with the help of 12 lead ECG. CRT devices were commonly programmed with an atrio-ventricular sensed delay of 110 ms and paced delay of 130 msec.

Echocardiography:

All patients underwent transthoracic echocardiography before and approximately 1 year after the CRT implantation. Patients underwent echocardiographic analyses in the left lateral decubitus position with a commercially available system (VIVID 7 Pro, GE-Vingmed Ultrasound AS N-3190, Horten, Norway). Images were obtained with a 2.5-MHz transducer in the parasternal and apical views (standard long-axis, two- and four-chamber windows). Standard two-dimensional and color Doppler data triggered to the electrocardiogram were saved in cine-loop format. LVEF was calculated from the apical two- and four-chamber images using the biplane Simpson's technique [11]. The severity of valvular pathology was evaluated and graded semi-quantitatively (scale 0–4) using color-flow Doppler [12].

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 21.0 (Statistical Package for Social Sciences) program. Continuous variables were given as mean ± standard deviation. The categorical data were given as median (%). For comparison of continuous variables between groups; the Student's T-tests were used for parametric tests, and the Mann-Whitney U tests were used for nonparametric ones. Chi-square tests were used to compare categorical data. Paired T-tests were used for continuous parameters such as QRS duration, LVEDD, and LVEF before and after CRT. Statistically significance was assumed as p value smaller than 0.05 for all tests.

RESULTS

56 patients (30 men and 26 women) were included in this study and the mean age was 57.5±9.7years. A biventricular ICD device with a left ventricular lead was implanted for each patient. The LV leads were implanted in the CS posterior vein for 21 patients, in the CS lateral vein for 23 patients, and in the CS postero-lateral vein for 12 patients. Demographic and basic data were shown in the Table 1.

Table 1. Comparison of patient characteristics according to QRS fragmentation (n=56)

Parameters	Fragmanted QRS(n=32)	Non-fragmented QRS (n=24)	p value
Age (years)	57.5±8.6	57.6±11.2	0.96
Gender, male n,%	17(%53.1)	13(%54.2)	0.94
Diabetes mellitus n,%	7(%21.9)	3(%12.5)	0.36
Hypertension n,%	16(%50)	10(%41.7)	0.53
Hyperlipidemia n,%	8(%25)	9(%37)	0.29
CKD n,%	3(%9.3)	2(%8.3)	0.94
Hemoglobin (gr/dl)	13.4±1.4	14.2±5.3	0.40
Creatinine(mg/dl)	0.96±0.41	0.9±0.23	0.52
NYHA mean pre-CRT	2.94±0.50	2.79±0.51	0.29
NYHA mean post-CRT	2.10±0.58	2.02±0.56	0.57
Diuretic n,%	31(%96.7)	24(%100)	0.88
ACE-inhibitors n,%	25(%78.1)	17(%70.8)	0.67
ARB n,%	5(%15.6)	5(%20.8)	0.46
B-blocker n,%	31(%96.7)	23(%95.8)	0.94
MRA n,%	29(%90.6)	22(%91.7)	0.92
Ivabradine n,%	2(%6.2)	1(%4.1)	0.84

Abb. *CKD; chronic kidney disease, NYHA; New York Heart Association, ACE; angiotensin converting enzyme, ARB; angiotensin receptor blocker, MRA; mineralocorticoid receptor antagonist, pre-CRT; pre–biventricular pacemaker implantation, post-CRT; at follow-up post–biventricular pacemaker implantation.*

fQRS was present in 32 (57.1%) patients. There were no statistically significant differences between the basal characteristics, clinical, electrocardiographic, and echocardiographic features of patients with and without fQRS (Table 1 and 2). A statistically significant increase in LVEF, TAPSE, peak systolic tricuspid annular velocity (St), and NYHA functional capacity was observed in both groups after CRT implantation. In addition, QRS duration, LVEDD, LVESD, mitral regurgitation (MR), and tricuspid regurgitation (TR) statistically significantly decreased (Table 3). However, no significant differences were found according to these parameters between the groups with and without fQRS (Table 2).

Table 2. Comparison of electrocardiographic and echocardiographic characteristics according to QRS fragmentation.

Parameters	Fragmented QRS(n=32)	Non-fragmented QRS (n=24)	p value
QRS width pre-CRT (ms)	153.2±11.0	150.5±16.9	0.46
QRS width post-CRT (ms)	125.9±13.6	123.9±15.3	0.61
LBBB n, %	28(%87)	22(%78.6)	0.86
LVEDD pre-CRT (mm)	67.0±7.1	69.5±8.6	0.24
LVEDDpost-CRT (mm)	60.3±8.1	63.8±8.6	0.30
LVESD pre-CRT (mm)	57.9±8.1	60.3±9.3	0.31
LVESDpost-CRT (mm)	49.5±9.9	52.8±9.6	0.21
LVEF pre-CRT(%)	26.9±5.2	25.6±4.8	0.41
LVEF post-CRT(%)	36.8±10.0	32.2±9.6	0.11
LVEFdifference (%)	9.8±9.2	6.6±4.2	0.12
TAPSE pre-CRT (cm)	1.68±0.41	1.82±0.43	0.55
TAPSE post-CRT (cm)	1.98±0.40	1.96±0.54	0.80
St pre-CRT(cm/sec)	10.6±2.7	11.3±3.6	0.49
St post-CRT (cm/sec)	12.5±3.3	12.2±4.0	0.75
SPAP pre-CRT (mm/Hg)	38.6±14.3	39.9±13.4	0.75
SPAP post-CRT (mm/Hg)	26.5±12.2	34.3±9.7	0.12
MRmean grade pre-CRT	1.72±0.95	1.79±1.21	0.80
MRmean grade post-CRT	1.19±0.64	1.29±1.08	0.66
TRmean grade pre-CRT	2.72±1.21	1.42±1.24	0.36
TRmean grade post-CRT	0.97±0.64	1.17±0.86	0.33

Abb. *LBBB; left bundle branch block, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEF; left ventricular ejection fraction, TAPSE; tricuspid annular plane systolic excursion, St; peak systolic tricuspid annular velocity, SPAP; systolic pulmonary artery pressure, MR; mitral regurgitation, TR; tricuspid regurgitation, pre-CRT; pre–biventricular pacemaker implantation, post-CRT; at follow-up post–biventricular pacemaker implantation*

Electrocardiographic, echocardiographic, and NYHA functional capacity changes before and after CRT implantation were examined and no statistically significant differences were found between the two groups (Table 4).

Although there was a decrease in QRS duration in 5 patients, a positive reverse remodeling and changes in functional capacities of the left ventricle were not observed. fQRS was present in 3 of these patients. In addition, LVEDD was higher than 70 mm in these patients and optimal medical treatment could not be given due to drug intolerance.

DISCUSSION

Cardiovascular morbidity and mortality increase with the presence of fQRS in the ECG. In contrast, CRT implantation has been shown to decrease cardiovascular morbidity and mortality. In the light of these data, we conducted this study to show whether CRT implantation has a better improvement effect on

Table 3. Comparison of baseline and the first year of QRS width, clinical and echocardiographic measurements according to QRS fragmentation

	Fragmented QRS (n=32)			Non-fragmented QRS (n=24)		
Parameters	Pre-CRT	Post-CRT	p value	Pre-CRT	Post-CRT	p value
QRS width (ms)	153.2±11.0	125.9±13.6	**<0.001**	150.5±16.9	123.9±15.3	**<0.001**
LVEF (%)	26.9±5.2	36.8±10.0	**<0.001**	25.6±4.8	32.2±9.6	**<0.001**
LVEDD (mm)	67.0±7.1	60.3±8.1	**<0.001**	69.5±8.6	63.8±8.6	**<0.001**
LVESD (mm)	57.9±8.1	49.5±9.9	**<0.001**	60.3±9.3	52.8±9.6	**<0.001**
TAPSE (cm)	1.68±0.41	1.98±0.40	**<0.001**	1.82±0.43	1.96±0.54	**<0.001**
St (cm/sec)	10.6±2.7	12.5±3.3	**<0.001**	11.3±3.6	12.2±4.0	**<0.001**
MR mean grade	1.72±0.95	1.19±0.64	**<0.001**	1.79±1.21	1.29±1.08	**<0.001**
TR mean grade	2.72±1.21	0.97±0.64	**<0.001**	1.42±1.24	1.17±0.86	**<0.001**
PABs (mm/Hg)	38.6±14.3	26.5±12.2	**<0.001**	39.9±13.4	34.3±9.7	**<0.001**
NYHA (mean)	2.94±0.5	2.1±0.58	**<0.001**	2.79±0.51	2.02±0.56	**<0.001**

Abb. LVEF; left ventricular ejection fraction, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, TAPSE; tricuspid annular plane systolic excursion, St; peak systolic tricuspid annular velocity, MR; mitral regurgitation, TR; tricuspid regurgitation, NYHA; New York Heart Association, pre-CRT; pre–biventricular pacemaker implantation, post-CRT; at follow-up post–biventricular pacemaker implantation.
Statistical significance was shown as bold.

mortality and morbidity in the NCMP fQRS patients. Although a significant improvement in QRS duration, NYHA class, and echocardiographic parameters was found in patients with NCMP and implanted CRT, statistical significance was not found between the two groups.

Table 4. Changes of the values of echocardiographic, electrocardiographic measurements and functional capacity after CRT implantation

Parameters	Fragmanted QRS	Non-fragmented QRS	p value
Delta QRS width (ms)	27.3±11.0	26.5±7.8	0.762
Delta LVEF %	6.8±5.9	4.3±4.4	0.155
Delta LVEDD (mm)	6.9±4.9	5±4.7	0.252
Delta LVESD (mm)	8.2±6.8	6.1±5	0.289
Delta TAPSE (cm)	3.2±3.1	1.3±2.4	0.155
Delta St (cm/sn)	2.3±2.7	0.1±1.3	0.058
Delta MR mean grade	0.5±0.7	0.4±0.9	0.882
Delta TY mean grade	0.7±0.8	0.4±1	0.248
Delta SPAP (mm/Hg)	13.6±16.3	6.8±10	0.191
Delta NYHA mean	0.9±0.6	0.8±0.6	0.590

Abb. LVEF; left ventricular ejection fraction, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, TAPSE; tricuspid annular plane systolic excursion, St; peak systolic tricuspid annular velocity, MR; mitral regurgitation, TR; tricuspid regurgitation, SPAP; systolic pulmonary artery pressure, NYHA; New York Heart Association

Cardiac resynchronization therapy is an effective method of treatment in patients with appropriate HF. The acute and long-term beneficial effects of the CRT have been demonstrated by previous studies [13-15]. However, about 30% of patients undergoing CRT implantation do not respond adequately, although they are selected according to existing patient selection criteria. Several reasons have been suggested in the literature for non-responsiveness to the CRT. Suboptimal lead position or lack of appropriate coronary sinus branch, presence of myocardial diffuse scar tissue, absence of echocardiographic dyssynchrony, irreversible advanced stage HF, and ischemic origin have been associated with non-responsiveness to the CRT [16].

fQRS has been associated with major adverse cardiac events in patients with ischemic or non-ischemic cardiomyopathy [17]. The presence of fQRS in patients with coronary artery disease was associated with more myocardial fibrosis, cardiac death, need for revascularization, ventricular arrhythmic events, all-cause mortality, and higher rates of myocardial infarction [18]. Moreover, fQRS has also a higher prevalence rate in patients with non-ischemic etiology such as sarcoidosis, hypertrophic cardiomyopathy, and non-ischemic heart failure [7].

The effect of the fQRS on the CRT response is a matter of curiosity in the literature so far. In a study conducted by Celikyurt et al., they found that the presence of fQRS was associated with poor outcomes in response to CRT [19]. Same results were also found in the other studies

conducted by Pranata et al., Liu et al., and Assadian Rad et al. [20-22]. In contrast, Rickard et al. demonstrated that the presence of fQRS was not associated with a negative response to CRT [23]. However, in these studies, study populations were not differentiated according to ischemic and non-ischemic etiology and most of the study populations were consisted of ischemic etiology. It is known that, although fQRS is a reflection of myocardial scar tissue on a 12-lead ECG, it can also be seen as a result of scar-independent electrical abnormalities [24]. Similarly, the fact that the presence of fQRS in our patient population is not related to the response to CRT may be due to the fact that fQRS is a reflection of the functional block, rather than a myocardial scar. In a study conducted by Sinsa et al. compared fQRS and non fQRS patients with NCMP by echocardiography parameters. They found that fQRS is associated with inter-ventricular dyssynchrony in the NCMP patients regardless of QRS duration [25]. Similar results were found in the study of Tigen et al. [26]. In accordance with that data, we aimed to compare fQRS and non fQRS in only non-ischemic cardiomyopathy patients for responsiveness of the CRT implantation. There was not statistically significance between groups. In addition, we compared the improvement of EF, QRS duration, LVEDD, TAPSE, St, MR and TR, SPAP, and NHYA classes after CRT implantation according to fQRS and non-fQRS. There was also not statistically significance between groups. This shows that fQRS do not affect the CRT response in NCMP patients.

In conclusion, the presence of fQRS is not an exact indicator of myocardial scar but can be seen due to functional electrical conduction delay. Therefore, it may be more useful to evaluate the presence of myocardial scar with additional imaging methods rather than the presence of fQRS alone in predicting the response after CRT implantation, especially in patients with non-ischemic heart failure.

Limitations

The present study has several limitations. Firstly this was a single-center experience with a limited number of patients. Secondly, we did not investigate intra- and inter-ventricular dyssynchrony in our study population. In addition, our study included patients who were symptomatic despite maximal medical therapy as recommended by the guideline. Patients without optimal medical therapy did not include and this may lead to bias. Thirdly, patients with sinus rhythm and isolated left or right bundle branch block were recruited. Although this situation restrained us from making exact predictions about other groups due to the small number of patients, evaluation in this specific patient group enabled us to exclude other confounding factors. Finally, our study does not include a myocardial scar assessment, which may be useful for determining the relationship between fQRS and scarring. Therefore, performing a larger multicenter study in which the presence of myocardial scar is confirmed by cardiac MRI may add more relevance to the data presented.

Conflict of Interest: None**.**

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