

Electrocardiographic Parameters as Predictors of Response to Cardiac Resynchronization Therapy

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Abstract

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INTRODUCTION: Although strict selection criteria are used to select patients for cardiac resynchronisation therapy, up to 30% of patients do not have a positive clinical response.

PATIENTS: A total of 102 consecutive patients who had biventricular pacemaker/defibrillator (CRT-P or CRT-D) implanted were enrolled in this prospective observational study.

RESULTS: During the average follow-up period of 24.3 months 5 patients died and 17 (16.7%) patients were hospitalised with the symptoms of heart failure; 75 (73.5%) patients were responders based on the previously defined criteria. Responders in the group of LBBB patients kept the significant difference in a computed variable $(S1 + R6) - (S6 + R1)$ and $R6/S6$ ratio. Responders in non-LBBB patients kept the significant difference only in the height of R waves in V6. The $R6/S6$ ratio tended to be higher, but it did not reach a statistical significance.

CONCLUSION: None of the tested ECG parameters stands out as an independent predictor of response to cardiac resynchronisation therapy, but some of them were different in responder-compared to the non-responder group. The amplitude of R wave in V6, higher R/S ratio in V6 and higher computed variable $(S1 + R6) - (S6 + R1)$ may predict the likelihood of response to CRT therapy in both LBBB-patients and non-LBBB patients.

Introduction

Cardiac resynchronization therapy (CRT), according to ESC Guidelines for diagnoses and treatment of acute and chronic heart failure (HF) is recommended for symptomatic patients in sinus rhythm, LBBB-QRS morphology and left ventricular ejection fraction (LVEF) $\leq 35\%$, despite optimal medical treatment, in order to improve symptoms and reduce morbidity and mortality [1][2]. If the QRS duration is ≥ 150 ms, it is class 1 indication for CRT implantation, LOE A, or if the QRS duration is 130-149 ms it is class 1 indication, LOE B. CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥ 150 ms and non-LBBB QRS morphology and may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130-149 ms and non-LBBB QRS

morphology [1]. For HF patients with atrial fibrillation (AF), the cut-off point for QRS duration is ≥ 130 ms (class IIa, LOE B) [1]. According to the same Guidelines CRT is contra-indicated in patients with a QRS duration < 130 ms, compared to 2013 guidelines on cardiac pacing and cardiac resynchronisation therapy where the cut-off point for QRS duration was 120 ms [3].

Despite very strong selection criteria and recommendation, up to 30% of patients after CRT implantation do not have a positive clinical response [4]. Responders are defined as patients who do better with the treatment rather than without it, regarding symptoms, physical activity, less frequent hospitalisations for HF etc. However, there is a poor correlation between clinical improvement and prognosis in heart failure patients. Variable response may be also due to differences in the underlying heart

disease. In the literature, there are few definitions of “responders”. Patients with NYHA-functional class III or IV could experience symptoms reduction, whereas the REVERSE trial showed no symptoms improvement in patients with functional class I or II compared to optimal drug therapy [5]. If we choose mortality as an endpoint or ventricular remodelling, or hospitalisation rate we will get a completely different picture of responders. Daubert C. *et al.* [6], in their practical guide to CRT, have proposed a definition of positive response as being alive with a sustained improvement in well-being, which for patients with moderate or severe HF means fewer hospitalisations and for patients with less advanced HF means no sign of disease progression. They have also suggested that remodelling of the left ventricle should be included in the global composite score, especially in patients with mild HF [6].

As predictors of non-response, several clinical and echocardiographic variables have emerged from previous studies. Ischemic aetiology, male gender, NYHA functional Class IV, severe mitral regurgitation, left atrial dilatation, and a short interventricular mechanical delay has been associated with worse clinical or echocardiographic outcomes [7][8].

Guidelines indicate that the QRS morphology is an important predictor of the therapeutic response to cardiac resynchronisation, giving a higher class to the patients with LBBB morphology in comparison to non-LBBB morphology patients. However, conventional criteria for diagnosing LBBB, including QRS duration > 120 msec, QS or rS in lead V1, and broad R waves, without Q waves in the lead I or V6 in the resynchronisation era seemed insufficient. ACC / AHA / HRS added notched, or slurred R wave in the lead I, aVL, V5 and V6, and occasional RS pattern in V5 and V6 attributed to the displaced transition of QRS complex [9]. It seems that prolonged duration of the QRS complex serves only as an indicator of the severity of the conduction disturbance [3].

Our study aimed to define more ECG criteria which can predict response to cardiac resynchronisation.

Patients and Methods

A total of 102 consecutive patients who had biventricular pacemaker/defibrillator (CRT-P or CRT-D) implanted at the University Clinic of Cardiology in Skopje, were enrolled in this prospective observational study. The indications for CRT were according to ESC Guidelines 2013 [3]: heart failure symptoms despite optimal medication; New York Heart Association (NYHA) functional class II-IV; LVEF \leq 35%; and QRS duration \geq 120 ms. Patients were followed for a mean of 24.3 months.

Surface 12-lead ECGs were acquired at a paper speed of 25 mm/s and a scale of 10 mm / mV at baseline and immediately after CRT device implantation. All ECGs were individually reviewed by two investigators. To assess the reproducibility as well as the reliability of the ECG measurements, we calculated the intra-and interclass correlation coefficient (ICC) by assessing 20 randomly selected images seen in two different occasions by the same or two investigators. The ICC for intra-observer variability was in the range 0.959 – 0.983 and for inter-observer variability was in the range 0.974 – 0.987. QRS duration was measured from its first deflection to its end. Left bundle branch block (LBBB) was defined as QRS duration > 120 msec, QS or rS form in V1 and broad R waves, without Q waves in the lead I or V6. Right bundle branch block (RBBB) was defined as QRS duration > 120msec, with qR or rSR form in V1 and deep S waves in the lead I and V6. Every other wide QRS without typical LBBB or RBBB morphology was classified as undetermined bundle branch (BB) morphology. From pre-implantation ECG we also analysed: R amplitude in V1 and V6, S amplitude in V1 and V6 and R6/S6 ratio and (S1 + R6) - (S6 + R1).

All patients underwent complete echocardiography examination at baseline, at 3-6 months and 12 months after CRT device implantation. Complete M-mode, 2-D, and Doppler evaluations were performed. Images were obtained in the parasternal and apical views. LV end-systolic volume, LV end-diastolic volume, and LVEF were calculated using the biplane Simpson’s technique.

CRT device implantation was performed by the standard transvenous procedure. The left ventricular (LV) lead was advanced to a lateral vein or, when it was unattainable, to a postero-lateral vein. The right ventricular (RV) lead was implanted in the apex of the right ventricle. In patients with the indication of ICD – implantation CRT-D device was implanted. The right atrial lead was implanted in the right auricular. All devices were programmed at a standard atrioventricular delay after implantation with optimisation using echocardiography usually performed 3-6 months after implantation. Medications were recorded immediately before implantation of the CRT device with titration of medications made at the discretion of the responsible cardiologist.

Definition of CRT Responder

Patients and implanted devices were followed up in the outpatient clinic at 1 month after implantation and then at 3-6 months. To define if the patient is responder at 6 months follow-up we used as the following parameters: increase in left ventricular ejection fraction (LVEF) more than 10%, lowering of NYHA class and on the other site hospitalisation for heart failure in 6 months after implantation. As non – responders were defined all patient who were not alive at 6 months follow-up and patients who have

hospitalisation for heart failure in this period and responders were all patients free of hospitalisation either with lowering of NYHA class or increase in LVEF more than 10%

Statistical analysis

Categorical parameters were summarised as percentages and continuous parameters as mean ± SD. Comparisons between the two groups were performed using the Student's t-test for continuous parameters and Pearson's chi-square test for categorical parameters. Assessment of correlation was done using Spearman's correlation analysis. Multiple logistic regression analysis was performed in stepwise order to determine independent predictors of OAC use.

All data analysis was performed using SPSS version 22.0 (IBM SPSS, Inc., Chicago, Illinois) and a p-value ≤ 0.05 was considered significant.

Results

Patients included in this study were with a mean age of 62.1 ± 9.6 years, predominantly male (57. 8%). Ischemic heart disease was the underlying aetiology of heart failure in 21.6% of patients and non-ischemic heart disease in 78.4% of patients. Before implantation 41.2% of patients were in NYHA functional class II, 48% in class III and 10.8% were in class IV. Baseline rhythm was sinus in 88.2% of patients, 8.8% were in permanent atrial fibrillation, and 2.9% had AV block of second or third degree. Mean duration of QRS complex was 171.9 ± 22.4 ms; 74.5% of patients had LBBB morphology, and in other/the remaining 25.5% non-typical BB morphology. None of the patients had RBBB morphology of QRS complex.

Implantation of the CRT device was successfully performed in all patients. A CRT-P device was implanted in 81.4% of patients, and CRT -D device in 18.6% of patients (74% of whom had ischemic aetiology of heart failure, P < 005).

During the average follow-up period of 24.3 months, from a total of 102 patients, 5 patients died, and 17 (16.7%) patients were hospitalised with symptoms of heart failure. Among 102 patients, 75 (73.5%) patients were responders based on the previously defined criteria.

The clinical characteristics of the responders and non-responders are summarised in Table 1.

There were no significant differences in age, sex, the aetiology of heart failure and presence of arterial hypertension. Responders were more likely to have lower BMI, lower NYHA class, less present atrial

fibrillation and diabetes mellitus and lower hospitalisation rate before CRT implantation compared to non-responders.

Table 1: Clinical characteristics of patients

	Responders (n = 75)	Non-responders (n = 27)	p-value
Age	61.5 ± 9.7	63.5 ± 9.2	n.s.
Gender (male %)	58.7%	55.6%	n.s.
BMI	24.9 ± 2.4	26.2 ± 2.1	0.012
Etiology of HF (ischemic /non-ischemic)	20% / 80%	26%/74%	n.s.
Atrial fibrillation	13.3%	33.3%	0.022
NYHA functional class	2.6 ± 0.6	3 ± 0.8	0.004
Arterial hypertension	48%	44.4%	
Diabetes mellitus	21.3%	48.1%	0.008
Hospitalization for HF prior to implantation	42.7%	70%	0.013

BMI - Body Mass Index; HF – Heart Failure; NYHA - New York Heart Association

Differences in ECG variables are listed in Table 2. There was no significant difference in QRS duration, the presence of LBBB or non-LBBB morphology of the QRS complex. Responders were more likely to have taller R waves and shorter S waves in V6, and bigger R6 / S6 ratio, compared to non-responders. The computed variable (S1 + R6) - (S6 + R1) was also significantly bigger in responders. Paced QRS duration was shorter in responders than in non-responders, but it did not reach a statistical significance.

Table 2: Electrocardiographic variables in responder and non-responder group

	Responders (n = 75)	Non-responders (n = 27)	p-value
PR interval	162.2 ± 23.0	182.2 ± 32.3	0.02
QRS duration	172.4 ± 21.9	170.7 ± 24.2	n.s.
LBBB morphology	77.3%	66.7%	n.s.
R amplitude in V1	1.1 ± 0.4	1.3 ± 0.5	0.04
S amplitude in V1	14.2 ± 5.9	14.5 ± 6.8	n.s.
R amplitude in V6	6.6 ± 5.0	3.6 ± 2.9	0.01
S amplitude in V6	4.1 ± 3.9	7.3 ± 6.6	0.01
R6/S6	4.6 ± 5.4	1.7 ± 2.5	0.02
(S1+R6)-(S6+R1)	15.7 ± 10.8	9.5 ± 8.8	0.02
Paced QRS duration	127.5 ± 26.3	137.0 ± 23.2	0.08

To find out if there is a difference in ECG parameters we divided the patient group in those with LBBB and those with non-LBBB morphology of the QRS complex. The ECG parameters of the responders and non-responders are summarised in Table 3.

Table 3: Electrocardiographic variables in different QRS morphology patients

	LBBB -patients			Non LBBB -patients		
	Responders	Non-responders	p-value	Responders	Non-responders	p-value
PR interval	163.6±24.2	180.7±36.1	n.s.	157.5±18.0	185±25.63	0.02
QRS duration	176.2±21.2	173.3±18.8	n.s.	159.5±19.8	165.6±33.2	n.s.
R amplitude in V1	1.1±0.4	1.4±0.5	n.s.	1.1±0.3	1.2±0.4	n.s.
S amplitude in V1	15.0±6.0	16.0±7.3	n.s.	12.1±5.1	11.2±3.7	n.s.
R amplitude in V6	7.7±5.2	4.7±3.0	0.01	3.3±2.5	1.3±0.8	0.01
S amplitude in V6	2.8±3.2	6.7±7.5	n.s.	7.6±3.7	8.5±4.5	n.s.
R6/S6	5.9±5.6	2.4±2.8	0.04	0.72±1.2	0.17±0.1	0.07
(S1+R6)-(S6+R1)	18.8±10.1	12.6±8.3	0.03	6.6±7.2	2.8±6.1	n.s.
Paced QRS duration	128.8±25.4	136.1±20.9	n.s.	122.9±29.7	138.9±28.5	n.s.

Responders in the group of LBBB patients kept the significant difference in a computed variable (S1 + R6) - (S6 + R1) and R6 / S6 ratio, probably due to a significant difference in height in R waves in V6.

On the other hand, responders in the group of non-LBBB patients kept the significant difference only in the height of R waves in V6. R6 / S6 ratio in this group of patients tended to be higher, similar to the LBBB patients, but it did not reach a statistical significance.

In both groups of patients, PR interval was longer in non-responders, but it reached statistical significance in non-LBBB group of patients.

Multivariate logistic regression analysis identified that none of the tested ECG parameters at baseline is an independent predictor of response to cardiac resynchronisation therapy.

Representative ECG of responders and non-responders with LBBB and non-LBBB morphology before implantation are shown in Figure 1.

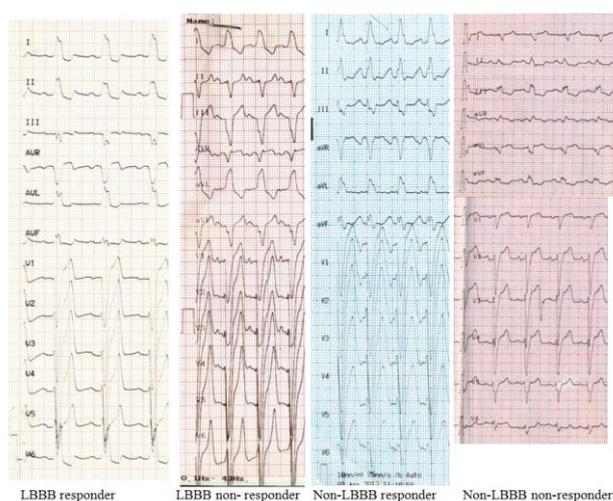


Figure 1: Representative electrocardiograms in responder and non-responder group

Discussion

The baseline QRS duration is a key part of the indication for cardiac resynchronisation therapy. It has been recognised since the publication of the Pacing Therapies in Congestive Heart Failure (PATH - CHF) I and II studies [10][11]. After publication of MADIT-CRT study in June 2009, FDA requested an additional 6 months of follow-up to see if the benefit of CRT-D persisted over time.

It was subsequently discovered and validated that the LBBB subgroup patients (approximately 70% of the total MADIT-CRT population) received substantial benefit from CRT-D. Non-LBBB patients did not show evidence of benefit [12]. During a sub-analysis, it was noticed that women more likely than men have LBBB [12]. Also, Sweeney *et al.* [13] have demonstrated that an LBBB-pattern of QRS is a strong predictor of response to CRT. This was further confirmed in the RAFT study [14]. LBBB configuration

of the ECG was accepted as a better predictor of CRT response than any of the echocardiographic parameters [15].

However, across the studies, approximately 30% of the implanted CRT patients have non-LBBB QRS morphology: 13% have RBBB morphology and 17% IVCD [16]. The MADIT – CRT study has shown that CRT implantation has led to more frequent heart failure events and death in patients with intraventricular conduction delay who received CRT - Defibrillators compared to implantable defibrillator alone [8]. As cardiac resynchronisation therapy is largely included in the management of patients with heart failure a need for a new definition of LBBB emerged, especially to distinguish LBBB from conduction delay due to left ventricular hypertrophy (LVH). New criteria for complete LBBB have been proposed, which include a terminal negative deflection in V1, QRS duration ≥ 140 ms for men and ≥ 130 ms for women (due to the size of the heart in different genders), and also mid-QRS notching or slurring in at least 2 of the leads I, aVL, V1, V2, V5 or V6 [17]. The presence of notching is very important in establishing the diagnosis of LBBB, and it should begin after the first 40 ms of the QRS, but before 50% of QRS duration, when the activation wave-front reaches the endocardium of the LV [17]. But, if the duration of QRS is long enough even in non-LBBB patients, the number of responders to CRT increases [18].

In our study 73.5% of patients were responders, and the rest of them were classified as non -responders. In the responder group, 22.7% of patients had non-LBBB morphology of the QRS, and opposite of that 66.7% of patients in the non - responder group had LBBB morphology of the QRS complex. Some of the studies suggest that patients with IVCD did not respond to CRT therapy [18][19]. The study of Takaya *et al.* (20) showed that 40% of patients with IVCD responded to CRT. This response rate was lower compared to large major trials, and the study concluded that patients with IVCD derive fewer benefits from CRT therapy regarding symptoms relief and echocardiographic findings [21][22].

ECG predictors in patients with LBBB and non-LBBB patterns

Mean QRS duration in our patient group was 171.9 ± 22.4 ms and we found no significant difference between non-responders and responders, or between LBBB and non-LBBB pattern of QRS. In both ECG patterns, paced QRS was wider in non - responder group compared to responder group, but this difference was not statistically significant. There is evidence in the literature that shortening of the QRS after CRT implantation is a predictor of response to CRT, even better than baseline QRS duration [23][24]. Lecoq *et al.* [24] reported that the only independent predictor of the CRT response is shortening of the QRS after CRT implantation. We found no statistical

significance of this parameter, but the results were in the same direction, confirming that changes in QRS duration after implantation may reflect the quality of electrical resynchronisation and the degree of correction of electromechanical abnormalities.

The pattern of ventricular activation sequence on ECG has been very rarely analysed as a predictor. In our study responders in LBBB-group showed a significant difference in amplitude of the R wave in V6, computed variable $(S1 + R6) - (S6 + R1)$ and $R6 / S6$ ratio. This finding is in concordance with the Strauss *et al.* [17] explanation of the real LBBB in comparison to EKG changes in case of left ventricular hypertrophy. Absolute and relative R wave amplitude in V6 could serve as a simple predictor of response to resynchronisation therapy in patients with LBBB morphology.

Responders in non-LBBB patients kept the significant difference only in the height of R waves in V6. $R6 / S6$ ratio in this group was higher, similar to LBBB patients, but it did not reach a statistical significance. Sweeney *et al.* [13] found that characterisation of ventricular activation sequence on the ECG anticipated the probability of response to CRT in patients with LBBB. They showed that QRS axis shifted from left to right, marked an increase in R-wave amplitudes in V1 through V2 on the ECG after device implantation, and predicted LV reverse remodelling.

Patients with non-LBBB pattern have delayed activation of either some or all of the right, left, or both ventricles. These patients may have less left-sided conduction delay than LBBB patients and therefore may not respond to CRT implantation. In the study of Takaya *et al.* [20], left axis deviation of QRS before implantation and QRS axis shift from left to right after implantation were found as predictors to CRT response.

Our study has clinical importance because it is one step forward in identifying patients who will respond to CRT therapy in a very simple way like an electrocardiographic recording.

Study limitations: This study is single centre experience, which is a limitation regarding treatment bias and could influence the outcome of the therapy.

The study is prospective, but with limited strength, because it is observational and has no control group. A small number of patients studied arises a need for confirmation in large prospective studies.

In conclusion, implantation of CRT device is a demandable procedure regarding sources, expertise and knowledge. The other part of the complexity is related to the disease itself, as heart failure is different and unpredictable in every single patient. Over the last decade, a majority of clinical studies have been focused on how to improve the selection of patients who will respond to this therapy-modality.

Our study gives a contribution to the proper patient selection by additional electrocardiographic criteria. Although none of the tested ECG parameters stands out as an independent predictor of response to cardiac resynchronisation therapy, some of them were clearly different in responder-group compared to the non-responder group. The amplitude of R wave in V6, higher R / S ratio in V6 and higher computed variable $(S1+R6) - (S6+R1)$ may predict the likelihood of response to CRT therapy in both, LBBB-patients and non-LBBB patients.

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