

Cardiac resynchronization therapy: QRS index as a response predictor

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Competing interests

The authors declare no competing interests

Abbreviations

CRT: cardiac resynchronization therapy

LV: left ventricle

LVEF: left ventricular ejection fraction

NYHA: New York Heart Association

ABSTRACT

Introduction: Cardiac resynchronization therapy (CRT) is an indication in heart failure with wide QRS and severely reduced left ventricular ejection fraction.

Objectives: To define the response predictors favorable to CRT.

Method: An observational, descriptive, retrospective study was conducted to evaluate the QRS index (difference between the QRS width before and after implantation, divided by its value before implantation, multiplied by 100) as a predictor of favorable response to CRT. Electrocardiograms were performed before the procedure, at 6 and 12 months after implantation. The measurements were made by two independent observers, the first digital on the operating room monitor and the rest manual.

Results: A total of 91 patients (mean age 61.2 years, 76% men) were included, with QRS wider than 120 ms and ejection fraction less than 35%. A favorable response was obtained in 59%. There were no significant pre-implant differences in the QRS duration between responders and non-responders (151.3 ms vs. 151.34 ms, $p=0.98$), but there were differences post-implant (100 vs. 115 ms, $p<0.0001$), as well as in the QRS percentage of decrease (33.2% vs. 24.3%, $p<0.0001$). The ROC curve showed that a cut-off value of the QRS index of 30% was sensitive (62%) and specific (75%) in order to predict a favorable response.

Conclusions: The decrease in the QRS width after the CRT implant is related to a favorable response to it.

Keywords: Heart failure, Cardiac resynchronization therapy, Electrocardiography, QRS index, Cuba

Terapia de resincronización cardíaca: Índice del QRS como predictor de respuesta

RESUMEN

Introducción: La terapia de resincronización cardíaca (TRC) es indicación en la insuficiencia cardíaca con QRS ancho y disminución grave de la fracción de eyección del ventrículo izquierdo.

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Objetivo: Definir los predictores de respuesta favorable a la TRC.

Método: Se realizó un estudio observacional, descriptivo, retrospectivo, para evaluar el índice del QRS (diferencia entre anchura del QRS antes y después del implante, dividido entre su valor antes del implante, multiplicado por 100) como predictor de respuesta favorable a la TRC. Se realizaron electrocardiogramas antes del procedimiento, a los 6 y a los 12 meses del implante. Las mediciones se hicieron por dos observadores independientes, la primera digital en el monitor del salón de operaciones y el resto manual.

Resultados: Se incluyeron 91 pacientes (edad media 61,2 años, 76% hombres), QRS mayor de 120 ms y fracción de eyección menor de 35%. Se obtuvo respuesta favorable en un 59%. No hubo diferencias significativas pre-implante en la duración del QRS entre respondedores y no respondedores (151,3 ms vs 151,34 ms, $p=0,98$), pero sí post-implante (100 vs 115 ms, $p<0,0001$), así como en el porcentaje de disminución del QRS (33,2% vs 24,3%, $p<0,0001$). La curva ROC mostró que un valor de corte del índice de QRS del 30% fue sensible (62%) y específico (75%), para predecir respuesta favorable.

Conclusiones: La disminución de la anchura del QRS luego del implante de la TRC se relaciona con una respuesta favorable a la misma.

Palabras clave: Insuficiencia cardíaca, Terapia de resincronización cardíaca, Electrocardiografía, Índice de QRS, Cuba

INTRODUCTION

The incidence and prevalence of heart failure has increased worldwide, probably due to population aging, reduced mortality from heart disease and increased survival of the population suffering from this disease owing to advances in its treatment¹.

Cardiac resynchronization therapy (CRT) has been recognized as a therapeutic option for patients with heart failure, wide QRS and severe left ventricular ejection fraction (LVEF) dysfunction, due to improved cardiac functioning², functional class according to the New York Heart Association (NYHA) and reduction of morbidity and mortality³.

QRS duration is part of the eligibility criteria for recommending CRT implantation although its role in the progression of heart failure remains poorly researched⁴. Despite proper implantation, not all patients respond favorably to treatment. In our research we sought to define the QRS index value as predictor of response to CRT.

METHODO

An observational, descriptive and retrospective study enrolling 91 consecutive patients treated with CRT, from September 2015 to February 2018, was carried out at the *Instituto de Cardiología y Cirugía*

Cardiovascular, Havana, Cuba.

Implant criteria were based on the current guidelines and follow-up was carried out at first, third, sixth and twelfth months after implantation. Clinical assessment, 12-lead electrocardiogram, two-dimensional transthoracic echocardiogram (at 6 and 12 months), and optimal drug treatment was maintained at each consultation.

The initial-post implant electrocardiographic measurement was performed digitally using a caliper of the CardioTek EP-Tracer Software version 1.05. Pre and post-implant measurements were made with a millimeter ruler by two independent observers, in a 12-lead electrocardiogram at 25 mm/sec scanning speed and 1 mV per mm amplitude.

Response to CRT was defined if it fulfilled the following criteria: an increase in NYHA functional class, 5% improvement in LVEF and 10% reduction in left ventricular end-systolic volume.

The QRS index was calculated using the formula: $[(\text{pre-implant QRS} - \text{post-implant QRS})/\text{pre-implant QRS}] \times 100$ (%); the lowest QRS duration obtained during follow-up was directly recorded.

Implantation protocol and CRT device programming

Device implantation was performed transvenously via the left subclavian route or tributary veins, and the generator was placed in the left pectoral region. Antibiotic treatment with Cefazolin was started (1

gram trans-procedure and then every 8 hours for 48 hours).

Active-fixation leads were positioned in the atrium and right ventricle and fixed to the left atrial appendage and apex, respectively. Bipolar left-ventricular leads (Biotronik Corox ProMRI OTW 75-BP, Medtronic Attain Ability 4196-88 cm, Medico Lifeline C.S. 750) were placed in a lateral or posterolateral position via coronary sinus, choosing the site with lower capture thresholds and absence of diaphragmatic stimulation. Generators from the Biotronik (Iforia 3 HF-T, Eluna 8 HF-T), Medtronic (Maximo II CRT-D, Syncra, C2TR01, Protecta XT CRT-D) and Medical (Helios 300) companies were used.

Pacing threshold, R-wave amplitude and impedance measurements were made throughout the procedure. The atrioventricular delay (A-V) was programmed between 100-120 milliseconds (ms), and also right to left ventricular activation delay (RV-LV), considering the shortest duration of the QRS complex.

The research was approved by the Institutional Ethics Committee. All ethical procedures related to the management of data sources were strictly followed throughout its development.

Statistical analysis

Numerical variables are shown as both mean and standard deviation, and categorical variables are expressed as frequencies and percentages. The Chi-square test (χ^2) was used to calculate differences between categorical variables, and the Student t test was used to calculate differences between numerical variables.

A ROC (receiver operating-characteristic) curve was performed to determine a cut-off value for the decrease index of the post-implant QRS complex, with sensitivity and specificity useful for predicting CRT response.

All statistical tests were performed at a significance level of 0.05. Statistical processing was performed with program (SPSS, Chicago Illinois, USA), version 11.5.

RESULTS

The average age was 61.2±11 years, with male predominance (75.8%); 97.8% with NYHA functional class III and 84.6% had complete left bundle branch

Table 1. Characteristics of pre-implant CRT patients.

Characteristics	Group of patients before CRT (n=91)	Responders (n=54)	Non-responders (n=37)	p
Age (mean ± DE)	61.2 ± 11	60 ± 11	63 ± 10	0.207
Male gender	69 (75.8)	40 (74.1)	29 (78.4)	0.415
Functional class II-III	89 (97.8)	52 (96.3)	37 (100)	0.349
Functional class IV	2 (2.2)	2 (3.7)	-	-
Severe mitral regurgitation	24 (26.4)	13 (24.1)	11 (29.7)	0.415
Prior PPM	10 (11.0)	7 (13.0)	3 (8.1)	0.356
CLBBB	77 (84.6)	44 (81.5)	33 (89.2)	0.243
Comorbidities				
Hypertension	31 (34.1)	18 (33.3)	13 (35.1)	0.517
Diabetes mellitus	13 (14.3)	9 (16.7)	4 (10.8)	0.321
Smoking	46 (50.5)	24 (44.4)	22 (59.5)	0.116
Alcoholism	11 (12.1)	5 (9.3)	6 (16.2)	0.249
Ischemic heart disease	45 (49.5)	21 (38.9)	24 (64.9)	0.013
Atrial fibrillation	11 (12.1)	6 (11.1)	5 (13.5)	0.486

Data express n (%), except for age.

CLBBB, Complete left bundle-branch block; CRT, cardiac resynchronization therapy; PPM, permanent pacemaker.

block; (the rest, had right bundle branch block). System upgrade was performed in 10 patients, and 70% responded favorably. A total 49.5% were is-chemic and 12.1% had chronic atrial fibrillation; 26.4% had severe mitral regurgitation (**Table 1**).

A total 54 of the 91 patients met the criteria for CRT responders (59.3%). The left ventricular end-systolic volume (LVESV) was the only variable of the responder group that was significantly higher than that of the non-responder group ($p=0.003$) within the pre-implant echocardiographic variables. Decreases in LV end-diastolic-and end-systolic diameters and LVESV at one year of follow-up was significantly higher in the responder group ($p<0.0001$; $p=0.001$ and $p=0.001$; respectively).

The sample had a mean of severely depressed LVEF and a marked prolongation of the QRS duration. The means of the LVESV and its pre-implant end-diastolic-and end-systolic diameters were high (**Table 2**).

The average FEVI increased by 6% in the group of CRT responders while in that of non-responders it increased by only 1.1%. ($p=0,001$).

Mean pre-implantation QRS duration was similar in both groups; while, at 12 months, this variable decreased significantly among patients with favorable response. Although the duration of the QRS was reduced in both groups, the responders group

showed a significantly higher QRS index (**Table 2**).

A ROC curve (**Figure**) based on the QRS index was performed, with an area under the curve of

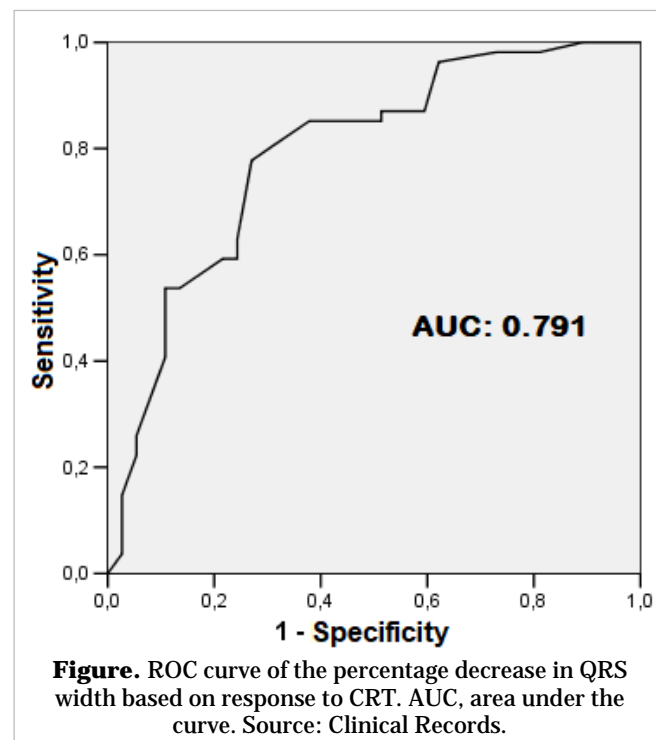


Figure. ROC curve of the percentage decrease in QRS width based on response to CRT. AUC, area under the curve. Source: Clinical Records.

Table 2. Distribution of echocardiographic and electrocardiographic variables according to response to CRT.

Variables	Pre CRT Total (n=91) (mean ± SD)	Responders (n=54) (mean ± SD)	Non-responders (n=37) (mean ± SD)	p*
Pre-implant LVEDD (mm)	74.6 ± 7.59	75.3 ± 8.00	73.5 ± 6.94	0.291
Post 12 months LVEDD (mm)	69.3 ± 7.2	66.8 ± 6.57	72.9 ± 6.73	<0.0001
Pre-implant LVESD (mm)	61.6 ± 7.89	61.8 ± 8.33	61.2 ± 7.30	0.724
LVESD post 12 meses (mm)	57.3 ± 7.4	55.28 ± 7.27	60.41 ± 6.57	0.001
Pre-implant LVESV (ml)	71.3 ± 7.62	73.0 ± 7.16	69.0 ± 7.75	0.013
Post 12 months LVESV (ml)	64.9 ± 7.5	62.9 ± 6.63	68.1 ± 7.91	0.001
Pre-implant LVEF (%)	25.4 ± 5.45	25.0 ± 5.47	26.1 ± 5.42	0.328
Post 12 months LVEF (%)	29.8 ± 5.4	31.4 ± 5.30	27.6 ± 4.88	0.001
Pre-CRT QRS duration (ms)	151.3 ± 12.6	151.3 ± 12.6	151.35 ± 12.9	0.98
Post-CRT QRS duration (ms)	106.7 ± 12.8	100.5 ± 10.44	115.7 ± 10.28	<0.0001
QRS Index (%)	29.6	33.25	24.35	<0.0001

* Statistical significance was calculated according to the variable among the groups of responders and non-responders.

CRT, cardiac resynchronization therapy; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume.

0.791. For a cut-off value of 30%, sensitivity of 62%, specificity of 75%, positive predictive value of 79% and negative predictive value of 58% were found. Two groups were defined ($\geq 30\%$ and $< 30\%$) and statistically significant differences were found between both in terms of response to CRT ($p < 0.0001$) (**Table 3**).

DISCUSSION

The usefulness of CRT for the treatment of heart failure with severe systolic LV dysfunction has been widely recognized in a number of studies⁶⁻⁸. It has been reported that nearly a 30% of patients undergoing CRT do not respond favorably⁹, therefore it is necessary to identify the predictors of response.

There was a 41% of non-responders in the series, although the literature reports a non-response rate between 30-40%, this figure tends to be lower due to the use of technologies such as multipoint pacing and deflectable vein sub-selectors, among others¹⁰.

In the present study, procedures were performed by means of long fixed-curve sheaths and bipolar leads, which would sometimes make it difficult to place the lead in the ideal place. Another element to consider is that almost half of the participants had a history of coronary artery disease, which was related to non-response, and 65% of them did not respond adequately to CRT.

According to current guidelines for cardiac pacing, the duration of QRS is the only marker of interventricular dyssynchrony used as a selection criterion for CRT⁵. The QRS duration prior to implantation has been identified as a favorable response predictor. Measurements greater than 150 ms have been associated with a lower risk of sudden death and worsening of heart failure at post-implantation follow-up^{6,11}.

In 2011, Rickard et al² were the first to relate the QRS index to a favorable response to CRT (OR 0.08 [0.01-0.56]; $p=0.01$); however, they did not show a cut-off point relating to an adequate response.

Subsequently, the same author published another study¹³, in 112 patients upgrading from right ventricular apical pacing to biventricular pacing where they considered a 15% reduction in VTSVI compared to baseline in response to CRT therapy, and found a

Table 3. Distribution of patients, according to the percentage decrease in the QRS complex index and response to CRT.

QRS Index	Response to CRT			
	Yes		No	
	Nº	%	Nº	%
$\geq 30\%$ (n=43)	34	79.1	9	20.9
$< 30\%$ (n=48)	20	41.7	28	58.3
Total (n=91)	54	59.3	37	40.7

$p < 0.0001$

higher percentage of decrease in QRS duration in responders than in non-responders ($14.4 \pm 13.2\%$ vs. $7.2 \pm 14.0\%$; $p=0.01$).

Coppola et al⁴ studied the effects of post-CRT QRS narrowing in 311 patients (67 ± 9 years, 72% men) and observed that the best cut-off value for the QRS narrowing index was 12.5% (test of logarithmic ranges [log-rank test], $p=0.0155$).

In another study of 61 patients, Molhoek et al¹⁵, showed that a decrease in QRS duration after CRT implantation of more than 10 ms, with respect to baseline figures has an acceptable sensitivity (73%) but low specificity (44%) to predict response to such therapy. The authors were unable to define an optimal cut-off value for reducing this measurement¹⁵.

The main finding of our study is that a cut-off point of 30% reduction in post-implantation QRS width is associated with a favorable response and acceptable sensitivity, specificity and predictive values. The baseline characteristics of the patients included in our study resemble those of other research, so it is believed that the results are easily reproducible in other implant centers. More importantly, the percentage of decrease in the QRS duration after CRT has been implanted, is a parameter that does not require expertise for its calculation, provides information at the time of implantation and does not increase expenses or surgical time.

CONCLUSIONS

A higher QRS index, which represents a decrease in the width of this complex, is related to a favorable response to CRT.

STUDY LIMITATIONS

This study has a number of limitations. First, the number of patients is not large enough to generalize our results; a larger sample is required to increase the statistical power of the investigation. Second, unfortunately, the coronary sinus vein used for LV lead implantation was not reported in the investigation, although posterolateral or lateral sinus veins were always chosen, but this data was not gathered in the data collection record. Third, the immediate post-implant value of the QRS width could be taken in future studies in a unique way, and be compared with pre-implant measurements in order to relate this data to the follow-up. In our research, the lowest QRS was taken either immediately after implantation or at 6 or 12 months. Finally, it is known that some patients respond late after the first year of implantation, our study only collected data up to 12 months after implanting the generator; to increase the statistical interest of the variable described (QRS width) these data can be taken in further assessment.

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