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**Original Article** 



# QRS dispersion as an index of dyssynchrony in left bundle branch block and of synchrony after cardiac resynchronization therapy: A variable of successful response

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#### ARTICLE INFORMATION

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Competing interests

The authors declare no competing interests

Acronyms

CHF: chronic heart failure CRT: cardiac resynchronization therapy LBBB: left bundle branch block LV: left ventricle LVEF: LV ejection fraction QRSd: QRS dispersion

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#### ABSTRACT

<u>Introduction</u>: Left bundle branch block is an important marker of poor prognosis in patients with heart failure. Resynchronization therapy can improve the function of the left ventricle in these cases.

<u>**Objective:</u>** To describe electrocardiographic variables associated with a better response to cardiac resynchronization.</u>

<u>Method</u>: A total of 19 patients, 7 women and 12 men, with left bundle branch block and ejection fraction  $\leq$  35% were studied. An electrocardiogram was performed before and after resynchronization therapy, with QRS measurement in the twelve leads and calculation of its dispersion. Maximum QRS voltages were also measured. An echocardiogram was performed before and after the procedure.

<u>**Results:**</u> The ejection fraction increased from 29.8±4.7 to 41.2±10.7 % (p=0.000). The linear correlation between ejection fraction and dispersion of QRS at six months of follow-up was significant (r=0.34 and p=0.02). Women showed a greater dispersion of QRS (48.0±24.0 ms vs. 37.14±13.8 ms; p=0.04). QRS voltages were predominantly negative in aVR (-0.52±0.58 vs. 0.28±0.42 mVolt; p=0.032) and positive in V<sub>5</sub> (0.71±1.12 vs. -0.15±1.20 mVolt; p=0.023) for responders in relation to non-responders.

<u>Conclusions</u>: The dispersion of QRS, increased in the electrocardiogram with left bundle branch block and decreased after resynchronization, showed a significant correlation with the ejection fraction. QRS narrowing after resynchronization was significant for responders. The predominantly positive voltages in aVR and negative in V<sub>5</sub> could adequately predict which patients will not respond adequately to cardiac resynchronization therapy.

*Key words:* Cardiac resynchronization therapy, Electrocardiogram, Heart failure, Left bundle branch block, Electrical dyssynchrony index, Left ventricle

*Palabras clave:* Terapia de resincronización cardíaca, Electrocardiograma, Insuficiencia cardíaca, Bloqueo de rama izquierda, Índice de disincronía eléctrica, Ventrículo izquierdo

# Dispersión del QRS como índice de disincronía en el bloqueo de rama izquierda y de sincronía tras la terapia de resincronización cardíaca, una variable de respuesta exitosa

#### RESUMEN

*Introducción:* En pacientes con insuficiencia cardíaca, el bloqueo de rama izquierda del haz de His constituye un importante marcador de mal pronóstico, en ellos la terapia de resincronización puede mejorar la función del ventrículo izquierdo.

**<u>Objetivo</u>**: Describir variables electrocardiográficas asociadas a una mejor respuesta de la resincronización cardíaca.

<u>Método</u>: Se estudiaron 19 pacientes, 7 mujeres y 12 hombres con bloqueo de rama izquierda y fracción de eyección  $\leq$  35 %. Se realizó electrocardiograma antes y después de la terapia de resincronización, medición del QRS en las doce derivaciones y cálculo de su dispersión, se midieron voltajes máximos del QRS, y se realizaron eco-cardiografías antes y después del procedimiento.

**<u>Resultados</u>:** La fracción de eyección se incrementó desde 29,8±4,7 hasta 41,2±10,7 % (p=0.000). La correlación lineal entre fracción de eyección y dispersión del QRS a los seis meses de seguimiento fue significativa (r=0.34 y p=0.02); las mujeres presentaron mayor dispersión del QRS (48,0±24,0 vs. 37,14±13,8 ms; p=0.04). Los voltajes del QRS fueron predominantemente negativos en aVR (-0,52±0,58 vs. 0,28±0,42 mvolt; p= 0.032) y positivos en V<sub>5</sub> (0,71±1,12 vs. -0,15±1,20 mvolt; p=0.023) para los respondedores en relación con los no respondedores.

**Conclusiones:** La dispersión del QRS incrementada en el electrocardiograma con bloqueo de rama izquierda y la disminución de la dispersión del QRS posresincronización demostraron correlaciones significativas con la fracción de eyección; además, el estrechamiento del QRS tras la resincronización fue significativo para los respondedores. Los voltajes predominantemente positivos en aVR y negativos en V<sub>5</sub>, pudieran predecir cuáles pacientes no responderán adecuadamente a la terapia de resincronización cardíaca.

*Palabras clave:* Terapia de resincronización cardíaca, Electrocardiograma, Insuficiencia cardíaca, Bloqueo de rama izquierda, Índice de disincronía eléctrica, Ventrículo izquierdo

#### INTRODUCTION

Chronic heart failure (CHF) remains a challenge for cardiology; its prevalence in the United States is estimated around 2.4% in adults. Despite optimal medical treatment, hospitalization for decompensation and death remain high in the first five years after its diagnosis<sup>1</sup>. Intraventricular conduction disorders are a powerful marker of poor prognosis in patients with CHF, particularly left bundle branch block (LBBB)<sup>2-4</sup>.

Cardiac asynchrony is complex and multifaceted. The prolongation of the atrioventricular (AV) interval delays systolic contraction, which could lead to early diastolic filling. Atrial pressure falls when the atria relax. If ventricular contraction is delayed, the diastolic pressure of the left ventricle (LV) exceeds atrial pressure and diastolic mitral regurgitation occurs. The loss of ventricular preload then leads to a reduction of LV contractility, by the loss of Starling mechanism. The delay of inter- and intraventricular conduction causes asynchronous contraction between regions of the LV wall (ventricular asynchrony), which affects efficiency and reduces cardiac stroke volume and systolic blood pressure. A poorly coordinated function of the papillary muscle can cause or aggravate functional systolic mitral regurgitation, and a deteriorated performance may lead to LV remodeling $^{5}$ .

Cardiac resynchronization therapy (CRT) helps restore AV synchronization and inter- and intraventricular synchronization. It improves LV function, reduces functional mitral regurgitation and induces reverse remodeling of LV, which is evidenced by increases in LV filling time and its ejection fraction (LVEF), and decreases in the end diastolic and systolic volumes of the LV, as well as a reduction of mitral insufficiency and septal dyskinesia. The dominant mechanism causing the benefit is likely to vary from one patient to another, and in the same patient, as time goes by. It is possible that no single measurement could accurately diagnose the response to CRT, since the benefit mechanisms are very heterogeneous<sup>5</sup>.

The MADIT-CRT and RAFT studies have shown the usefulness of CRT in patients with CHF and LBBB<sup>4,6</sup>. The pursuit of clinical, electrocardiographic, echocardiographic parameters and programmable values, such as the AV and interventricular (VV) intervals of the CRT devices, have been the focus of attention of electrophysiologists, since the beginning of this electrical therapy, to identify the ideal candidate to be a responder to CRT<sup>8-12</sup>.

Despite these efforts, 20 to 40% of patients who receive a CRT device continue to show a non-favorable response to this form of treatment<sup>13</sup>.

At the Cardiocentro Ernesto Che Guevara, the implantation of CRT devices started at the beginning of 2010; approximately 6-10 devices were implanted per year, always considering expert opinion and the guidelines for the selection of patients. These criteria have changed with the results of the different studies so far mentioned. In our hospital, an average of 15 to 20 devices is implanted per million inhabitants. The objective of this study is to describe preliminary results of electrocardiographic variables which are associated with a better response to CRT.

## METHOD

A prospective study was conducted with 19 patients, from a total of 23, who received a CRT device at the Cardiocentro Ernesto Che Guevara in Santa Clara, Cuba, from January 2010 to June 2014. The minimum follow-up period was 11 months. The variables included in the study belong to the first six months.

This study was approved by the Ethics Committee and the Scientific Council of the above mentioned hos-

pital.

## **Inclusion criteria**

- 1. Patients with left bundle branch block and QRS > 120 milliseconds (ms) and sinus rhythm.
- 2. LVEF ≤ 35%.
- 3. No evidence of pulmonary hypertension, ruled out by echocardiography.
- 4. Angiographically normal epicardial coronary arteries, without atherosclerotic lesions.
- 5. No clinical evidence when questioned about coronary artery disease.
- 6. Coronary sinus electrode placed in the left lateral vein.
- 7. New York Heart Association (NYHA) Functional Class II-IV, with outpatient treatment.
- 8. Failure to respond to optimal medical therapy.

## Monitoring and exclusion

Patients were treated in the outpatient department at one week, one month, three months and six months after device implantation. Of the 23 patients, 4 were excluded for the following reasons:

- CRT with chronic atrial fibrillation and proven coronary artery disease: 1
- Death from cardiac decompensation: 1
- LV electrode which was not placed in the lateral vein: 2

## Echocardiogram

Classic echocardiography criteria for including patients were initially considered according to the 2007 guidelines<sup>14</sup>. In 2010, an update of these guidelines was carried out and the echocardiography passed into the background, therefore the calculation of the LVEF by the Simpson method and the area-length method was of interest. Pressures of the pulmonary artery trunk<sup>15</sup> were also estimated, and LVEF, LV end-diastolic diameter and its end-systolic volume were calculated before the implantation of CRT device and six months later. These variables were useful to classify patients into responders or non-responders to CRT.

## Electrocardiogram (ECG)

ECG with LBBB and QRS duration > 120 ms for NYHA functional class III-IV and QRS>150 ms for patients with NYHA functional class II, according to the 2010 update of the guidelines, which was the date when the study started<sup>15</sup>. QRS manual measurement was per-

formed in the 12-lead of the ECG, recorded in unison, standardized, where 10 millimeters (mm) equals 1 millivolt and the paper speed was 25 mm/second. The QRS was measured from the initial deflection of the wave to its completion at point J. The difference in measurement of the widest QRS (wQRS) minus the narrowest QRS (nQRS) was calculated and the variable QRS dispersion (QRSd) was determined.

#### Formula: QRSd = wQRS - nQRS

Immediately after implantation, the following parameters were programmed into the device: synchronous VV and AV delay between 100 and 120 ms, the latter depending on the AV conduction with LBBB. If AV conduction with LBBB was equal to or less than 130 ms, it was programmed to 100 ms; if it was greater than 130 ms, it was programmed to 120 ms. Once these two parameters were programmed, an ECG was performed where QRSd was calculated.

In the twelve leads, the highest QRS voltage was measured, since its inception in the baseline to the top of the R wave or the nadir of the S wave.

#### Selection of responders and non-responders

Patients with a LV end-systolic volume decrease >15%, a 5% increase of LVEF and functional class improvement (tested with a walk of 6 minutes) were considered responders. Patients who did not achieve the above mentioned values were considered non-re-

## sponders.

#### **Statistical analysis**

A database created with the SPSS version 17.0 for Windows was used. The normal distribution of the sample was checked and p>0.05 was obtained for the Shapiro-Wilk test, which allowed us to perform other parametric tests. A frequency distribution of the numerical variables in the study was carried out; and mean and linear regression comparisons were performed to test for statistical association: significant (p<0.05), highly significant (p<0.001) and not significant (p>0.05).

# RESULTS

Twelve men and 7 women were studied (**Table 1**). All women were responders to CRT and only 4 men (21%) were non-responders. The mean LVEF before CRT was similar for both sexes and for the groups of responders and non-responders, from 29.2 to 30.6%. The increase in terms of the mean LVEF in responders was slightly higher in the group of women (47.2 vs. 42.4%) with no significant difference (p=0.262). The group of nonresponders showed a drop in the mean LVEF. The increase of this variable for the whole sample was from  $29.8\pm4.70\%$  to  $41.2\pm10.7\%$ , p=0.000.

The QRSd (**Table 2**) with LBBB showed a higher value in female responders compared to male responders  $(40.0\pm28.0 \text{ vs. } 48.0\pm24.0 \text{ ms})$ ; however, it did not show significant differences (p>0.05). Immediately after the

Table 1. Distribution of patients by sex, mean age, response to CRT and mean LVEF before and six months after devi	ice
implantation.	

	Sex		<b>A</b> .co	LVEF		
Response			Age		Before CRT	Before CRT
		N⁰	%	χ±DE	χ ± SD	χ ± SD
Descradence	Female	7	36.8	51.4 ±15.01	29.8 ± 7.35	47.2 ± 7.04
Responders	Male	8	42.1	59.0 ± 7.07	29.2 ± 6.01	42.4 ± 7.97
No	Female	0	0	-	-	-
Non-responders	Male	4	21.0	43.0 ± 1.41	30.6 ± 2.50	22.8 ± 1.34
	Female	7	36.8	51.4 ± 15.01	29.8 ± 7.35	47.2 ± 7.04
Both	Male	12	63.1	54.43 ± 9.72	29.8 ± 4.59	37.5 ± 11.3
Total		19	100	53.1 ± 11.6	29.8 ± 4.70	41.2 ± 10.7

χ, mean; SD, standard deviation

 $p \ge 0.05$  for comparisons of mean LVEF according to sex in responders.

 $p \ge 0.05$  for comparisons of mean age according to sex.

implantation, according to the response to CR1.						
Response	Sex		QRS dispersion With LBBB With LBBB			
·		N⁰	%	χ ± SD	χ±SD	
Responders	Female	7	36.8	48.0 ± 24.0	24.0 ± 8.9	
	Male	8	42.1	40.0 ± 28.0	28.0 ± 10.9	
N 1	Female	0	0	-	-	
Non-responders	Male	4	21.0	30.0 ± 14.1	30.0 ± 14.1	
Both (Total)	Female	7	36.8	48.0 ± 24.0	24.0 ± 8.9	
	Male	12	63.1	37.14 ± 13.8	28.57 ± 10.6	

**Table 2.** Distribution of mean QRS dispersion before and immediately after device implantation, according to the response to CRT.

χ, mean; SD, standard deviation

p>0.05 for all mean comparisons between responders and non-responders

p=0.000 for comparisons of mean QRSd before and after CRT in responders.

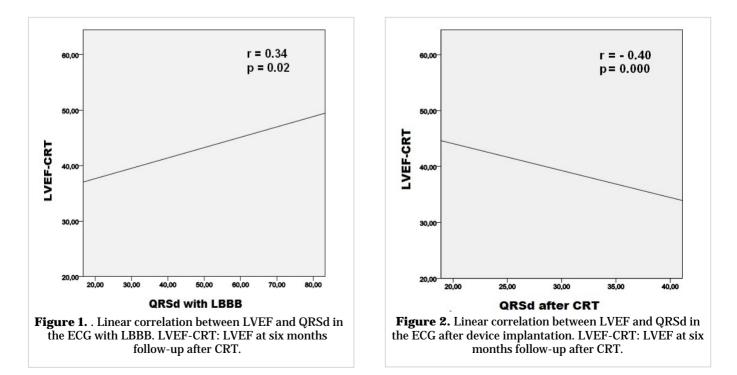
p=0.04 for comparisons of QRSd before the CRT (with LBBB) by sex in responders.

device was implanted and reprogrammed, as explained in the method, an ECG was performed and the QRSd was calculated; note that the decrease in QRSd in men who were responders was 28.0±10.9 ms and 24.0±8.9 ms in women (p=0.234). Comparisons of mean QRSd, with LBBB and after resynchronization, regarding sex (40.0±28.0 vs. 28.0±10.9 ms for men and 48.0±24.0 vs. 24.0±8.9 ms for women) showed significant differences (p=0.000). When comparing the mean QRSd, for the whole sample in the study, it was  $37.14\pm13.8$  in male vs.  $48.0\pm24.0$  ms in female patients, showing significant differences (p=0.04). In the group of non-responders this QRSd value ( $30.0 \pm 14.1$  ms) was unchanged.

For the group of responders, a linear correlation between LVEF at six months of follow-up (**Figure 1**), as the dependent variable, and QRSd with LBBB, as independent variable, showed a correlation coefficient r=0.34 and p= 0.02. The same statistical test

was applied to responders, between LVEF at six months of follow-up and QRSd in the ECG after CRT (**Figure 2**) and it was found that the LVEF increased as QRSd decreased (r=-0.40 y p=0.000).

The distribution of mean values for the widest QRS, measured with LBBB, and measured immediately after CRT, is shown in **Table 3**. The group of responders had a mean widest QRS higher than non-responders (172.7±



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16.1 vs.  $150\pm14.1$  ms), with no significant differences (p>0.05). Once the device was implanted, the QRS narrowed in responders from  $172.7\pm16.1$  to  $105\pm13.8$  ms (p=0.000). The decrease in the mean QRS width for non-responders was up to 120 ms, showing no significant difference (p>0.05).

QRS voltage in the twelve leads identified differences in some of them (L<sub>1</sub>, aVL, aVR, V<sub>5</sub>) depending on the group of patients (responders or non-responders) (**Table 4**). Responders showed higher voltages of the R wave in LI than non-responders ( $0.71\pm0.17$  vs.  $0.27\pm0.17$  mVolt; p=0.008), it was the same with the voltage of R wave in aVL ( $0.68\pm0.25$  vs.  $0.10\pm0.14$  mVolt; p=0.045). QRS voltage in aVR, in responders, was predominantly negative, compared to non-responders who had a positive QRS voltage ( $-0.52\pm0.58$  vs.  $0.28\pm0.42$  mVolt; p=0.032). For V<sub>5</sub> the mean QRS was posi-

tive, with an R wave of 0.71±1.12 mVolt, when compared with non-responders who predominantly had negative QRS (-0.15±1.20 mVolt; p=0.023).

#### DISCUSSION

All the women selected for our study were responders to CRT. The 2013 Clinical Practice Guidelines of the European Society of Cardiology on stimulation and cardiac resynchronization therapy, when explaining the possibilities of better response to CRT, say that the criteria set out in the guide represent the view of the majority of the working group, but not all those who contributed agreed. Several statements are based on subgroup analysis of randomized clinical trials, which poses many problems of interpretation (interrelation between morphology and QRS duration, differences in response depending on sex, diagnostic benefit in ischemic or non-ischemic patients) and areas of uncertainty that are still under study (potential role of echocardiographic asynchrony in the narrow QRS). And they conclude that future studies

might change knowledge and recommendations<sup>5</sup>.

In our opinion, they enumerate a set of criteria which demonstrates that there is heterogeneity in the selection of samples in CRT studies. In order to homogenize our sample (see inclusion criteria), our study included 19 patients without clinical reference of coronary artery disease, with epicardial arteries without angiographic lesions and the LV electrode placed on the lateral vein. However, despite this attempt to homogenize, the whole group of women studied responded to the CRT; whereas only 66% of men were responders. Women accounted for 36.8% of the total sample.

Xu *et al*<sup>16</sup>, mentioned in their study, which coincides with our results in percentage terms, that the percentage of women with CRT who have been studied has always been lower in most of the investiga-

Table 3.	Distribution of mean values for the widest QRS measured with LBBB
	and immediately after resynchronization.

	Widest QRS (mVolts)			
Response	With LBBB χ±SD	With LBBB χ±SD		
Responders	172.7 ± 16.1	105.4 ± 13.8		
Non-responders	150.0 ± 14.1	120.0 ± 0.00		
Total	169.2 ± 17.5	107.6 ± 22.4		

χ, mean; SD, standard deviation

 $p \ge 0.05$  for all mean comparisons between responders and non-responders.

p=0.000 for comparisons of mean widest QRS with LBBB and after resynchronization in responders.

Table 4.	Distribution of mean values for the highest QRS voltages in some ECG
	leads, according to the response to CRT.

Response	Highest voltage of QRS with LBBB (mVolts) (χ ± DE)				
	L <sub>I</sub> *	aVL**	aVR <sup>Ω</sup>	$V_5^{\Omega\Omega}$	
Responders	0.71 ± 0.17	0.68 ± 0.25	-0.52 ± 0.58	0.71 ± 1.12	
Non-responders	0.27 ± 0.17	$0.10 \pm 0.14$	$0.28 \pm 0.42$	-0.15 ± 1.20	
Total	0.65 ± 0.23	0.59 ± 0.40	-0.43 ± 0.58	0.58 ± 1.13	
$\chi$ , mean; SD, standard deviation * p=0.008 $^{\Omega}$ p=0.032					

p=0.003 p=0.032\*\* p=0.045  $\Omega\Omega$  p=0.023

\* p=0.045 p=0.023

tions; they also state that both sexes have an equally significant response to CRT with regard to the increase in LVEF. This also coincides with our results, because although women had higher LVEF that responder men (47.2 vs. 42.4%), there was no significant differences. However, Varma *et al*<sup>17</sup> showed gender differences in describing that, with a QRS>150 ms, 86% of women responded to CRT vs. 36% of men, and with a QRS <150 ms, 83% of women vs. 69% of men. Loring *et al*<sup>18</sup>, suggest that the better response of women to CRT may be due to a greater number of false positives when selecting LBBB in males and not to differences in other already studied variables.

No reports mentioning the study of QRSd were found in the reviewed literature<sup>1-48</sup>. When reflecting on the existing theory of P wave dispersion on the ECG<sup>39-41</sup>, which explains regional differences in the atrial activation times with intra- and interatrial conduction disorders, it is thought that in the presence of LBBB, where electrical delays of some areas of the heart have been demonstrated—for example the LV lateral wall with respect to the interventricular septum<sup>5,18</sup>—there could also be minimum and maximum QRS duration values which could allow us to calculate the dispersion. Therefore, we decided to study this new variable.

The preliminary observation we can mention is the larger QRSd in females (100% responders to CRT), as well as the decrease in this QRSd, when comparing the ECG before (with LBBB) and immediately after the CRT, which was more evident in women; in addition to the significant correlations of LVEF with QRSd on the follow-up echocardiogram. This could be a new variable to be assessed in future studies; that is, QRSd, which showed in our research that a larger QRSd on the ECG with LBBB (before CRT) and a greater regression of the dispersion value after CRT are related with greater increases in LVEF and improvement of the functional class. In other words, it could be said that QRSd can become an excellent variable to predict the outcome of CRT.

It is proposed to name the QRSd: **electrical dyssynchrony index of the LV in the presence of left bundle branch block**. The preliminary results presented here demonstrate the existence of a larger QRSd in patients with the widest QRS in the presence of LBBB; and the existence of higher electrical dyssynchrony in patients with QRS>150 ms has been proven<sup>5,17,18</sup>. This aspect was highlighted by Varma<sup>42</sup> in 2009, demonstrating delays in the activation of the left ventricle. In addition, the regression of QRSd is higher in those patients who respond favorably to the CRT, which may be associated with the restoration of electrical synchrony and would have to be demonstrated from an electrophysiological point of view. It was also noted that the widest leads were LI and aVL; results that are not shown in this article, and will be published later.

The width of QRS has always been a matter of interest to select those patients who are responders or not to CRT. In the guidelines<sup>5,14,15</sup> the benefit of this treatment in patients with LBBB>150 ms is mentioned <sup>5,38</sup>. It has been considered that a QRS lower than 130 ms may predict a poor response to CRT<sup>43</sup>.

Dupont et al<sup>44</sup> highlight the importance of morphology and QRS duration to get a better response to CRT, they considered 150 ms as a cutoff, although it must be said that, in their study, the patients with LBBB and QRS>150 ms had a 12±12% increase in LVEF and those with QRS<150 ms had a 8±10% increase in LVEF; therefore, as the increase in LVEF was greater than 5% in both groups, both should be considered as responders, although the authors found significant difference between these values (p<0.05). However, Guglin and Curtis<sup>45</sup>, have argued that it is reasonable to expect that the longer the QRS the better the patient' response to CRT, because the electrical dyssynchrony between the septum and the LV lateral wall is bigger. They also mention that current studies have shown increases in LVEF from 28.4±7.3% to 33.9±9.7% (p<0.001) in patients with QRS between 120 and 150 ms, and from 26.0±12.9% to 37.0±12.5% (p<0.001) in patients with QRS>150ms, demonstrating that, in these two groups, the increase in LVEF was approximately 5.5±7.3% vs. 11.0±12.1% (p=0.04); therefore, the possibility that patients with LBBB and QRS between 120-150 ms may be good responders to CRT cannot be ruled out. For this reason, they think it is better to continue studying these differences or simply divide the groups into small increases in LVEF and finally consider that 150 ms is not a magic number for selecting a patient for CRT. The initial reduction of QRS width after CRT was recorded in the REVERSE study as an indicator of good response to this type of electric therapy<sup>46</sup>. Our results agree with these proposals, because it was found a significant decrease in QRS width in responders (a mean reduction of 67 ms), while nonresponders had a reduction of only 30 ms.

QRS morphology is also associated with a good re-

sponse to CRT<sup>46,47</sup>. Patients with a clear LBBB meet-ing the criteria for this intraventricular conduction disorder have proven to be the best responders to CRT. The same has been said about patients with LBBB without axial deviation of the QRS axis to the right or to the left; they are better responders<sup>10</sup>.

Our results show that responders are within normal voltages in the leads of the frontal and horizontal planes [L<sub>1</sub>, aVL, aVR, V<sub>5</sub> (**Table 4**)]. Deviations from the QRS electrical axis orientation were not found; it was only observed that in responders there is tendency to have normal voltages in the aforementioned leads. Non-responders had lower positive voltages in the leads of frontal plane (L<sub>1</sub> and aVL), and predominantly positive voltages in aVR and negative voltages in V<sub>5</sub>, the latter denoted a poor upward progression of R wave voltage in precordial leads (up to V<sub>5</sub>) in non-responders.

García-Seara et al<sup>48</sup>, observed that patients with LBBB and left axial deviation of the electrical axis, who had the LV electrode placed in the lateral vein, had a better response to CRT. However, Brenyo et al<sup>10</sup> showed that patients with LBBB without left axial deviation of the QRS axis had the best response to CRT. Loring et al<sup>18</sup> concluded that the differences between men and women in the response to CRT are not associated with comorbidity, as they showed that non-responders did not have an ECG with real criteria for LBBB, but had similar electrocardiographic patterns which could be justified by delays of the left intraventricular conduction. Perhaps the differences in QRS voltages for non-responders, in the leads studied in our sample, are related to other left intraventricular conduction disorder and not a true LBBB.

In addition to the above, Josephson and Wellens<sup>49</sup>, in Josephson Wellens ECG Lessons: A monthly visit to the 12 lead ECG have argued that the presence of a positive terminal R wave in aVR and a negative predominance in  $V_5$  (R/S <1) is associated to growth or involvement of the right ventricle. They also mentioned that if these findings are chronic, they can predict a poor response to CRT.

# CONCLUSIONS

The ECG continues to be a useful tool for selecting patients for CRT. A larger QRSd in the ECG with LBBB had a significant association with the increase of LVEF six months after CRT. The significant reduction of QRSd after CRT showed a significant correlation with the increase in LVEF during the follow up. Women had higher QRSd values in the ECG with LBBB and proved to be the best responders to CRT. The narrowing of the QRS after CRT, which coincides with the reduction of QRSd, was significant in responders. Patients with predominantly positive voltages in aVR and negative voltages in V5 did not respond adequately to CRT, something that may be useful in selecting patients for this treatment. The QRSd could be a useful variable to predict the response to CRT.

# STUDY LIMITATIONS

This study was conducted with a small sample, with implantation of the LV electrode in the lateral vein. It did not include functional tests of great importance, such as single-photon emission computed tomography or nuclear magnetic resonance to rule out the presence of coronary artery disease; so its absence was only determined by clinical symptoms and coronary angiography. Therefore, the results obtained here need to be reproduced and evaluated in samples with different characteristics and comorbidities. Furthermore, other electro and echocardiographic variables which are widely mentioned in the literature reviewed were not assessed. Finally, failing to check the possible relationship between the widest QRS, QRS dispersion and LV electrical dyssynchrony was also a limitation.

## REFERENCES

- Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, *et al*. Heart disease and stroke statistics – 2011 update: A report from the American Heart Association. Circulation. 2011;123:e18-e209.
- 2. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C, *et al.* Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol. 2008;52:1834-43.
- 3. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, *et al*. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361:1329-38.
- Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, *et al*. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010;363:2385-95.
- 5. Brignole M, Auricchio A, Barón-Esquivias G, Bordachar P, Boriani G, Breithardt OA, *et al*. Guía de prác-

tica clínica de la ESC 2013 sobre estimulación cardiaca y terapia de resincronización cardiaca. Rev Esp Cardiol. 2014;67:58.e1-e60.

- 6. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, *et al.* Effectiveness of cardiac resynchronization therapy by QRS morphology in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT). Circulation. 2011;123:1061-72.
- 7. Cuoco FA, Gold MR. Optimization of cardiac resynchronization therapy: Importance of programmed parameters. J Cardiovasc Electrophysiol. 2012;23: 110-8.
- Holmqvist F, Daubert JP. More bad news for cardiac resynchronization therapy in atrial fibrillation patients: What to do? J Cardiovasc Electrophysiol. 2013;24:1123-4.
- 9. Sebag FA, Martins RP, Defaye P, Hidden-Lucet F, Mabo P, Daubert JC, *et al.* Reverse electrical remodeling by cardiac resynchronization therapy: Prevalence and clinical impact. J Cardiovasc Electrophysiol. 2012;23:1219-27.
- 10.Brenyo A, Rao M, Barsheshet A, Cannom D, Quesada A, McNitt S, *et al.* QRS axis and the benefit of cardiac resynchronization therapy in patients with mildly symptomatic heart failure enrolled in MADIT-CRT. J Cardiovasc Electrophysiol. 2013;24: 442-8.
- 11.Cochet H, Denis A, Ploux S, Lumens J, Amraoui S, Derval N, *et al*. Pre- and intra-procedural predictors of reverse remodeling after cardiac resynchronization therapy: An MRI Study. J Cardiovasc Electrophysiol. 2013;24:682-91.
- 12.Arbelo E, Tolosana JM, Trucco E, Penela D, Borràs R, Doltra A, *et al.* Fusion-optimized intervals (FOI): a new method to achieve the narrowest QRS for optimization of the AV and VV intervals in patients undergoing cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2014;25:283-92.
- 13.Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, *et al*. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346:1845-53.
- 14.Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, *et al*. Guidelines for cardiac pacing and cardiac resynchronization therapy: The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart

Rhythm Association. Eur Heart J. 2007;28: 2256-95.

- 15.Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, *et al.* 2010 focused update of ESC Guidelines on device therapy in heart failure: An update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC Guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Eur Heart J. 2010;31:2677-87.
- 16.Xu YZ, Friedman PA, Webster T, Brooke K, Hodge DO, Wiste HJ, *et al*. Cardiac resynchronization therapy: Do women benefit more than men? J Cardiovasc Electrophysiol. 2012;23:172-8.
- 17.Varma N, Manne M, Nguyen D, He J, Niebauer M, Tchou P. Probability and magnitude of response to cardiac resynchronization therapy according to QRS duration and gender in nonischemic cardiomyopathy and LBBB. Heart Rhythm. 2014;11:1139-47.
- 18.Loring Z, Caños DA, Selzman K, Herz ND, Silverman H, MaCurdy TE, *et al.* Left bundle branch block predicts better survival in women than men receiving cardiac resynchronization therapy: long-term follow-up of ~ 145,000 patients. JACC Heart Fail. 2013;1:237-44.
- 19.Ford J, Sears S, Ramza B, Reynolds DW, Nguyen P, Fedewa M, *et al.* The Registry Evaluating Functional Outcomes of Resynchronization Management (REFORM): Quality of life and psychological functioning in patients receiving cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2014;25: 43-51.
- 20.Lindsay BD. Perspective on cost-effective utilization of cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2013;24:75-6.
- 21.Hayat SA, Kojodjojo P, Mason A, Benfield A, Wright I, Whinnett Z, *et al*. Malfunction of subpectorally implanted cardiac resynchronization therapy defibrillators due to weakened header bond. J Cardiovasc Electrophysiol. 2013;24:351-5.
- 22.Doguet F, Honoré C, Godin B, Anselme F. Isolation of the phrenic nerve to suppress diaphragmatic contraction induced by cardiac resynchronization. J Cardiovasc Electrophysiol. 2012;23:778-80.
- 23.D'Onofrio A, Botto G, Mantica M, La Rosa C, Occhetta E, Verlato R, *et al.* Incremental value of larger interventricular conduction time in improving cardiac resynchronization therapy outcome in pa-

tients with different QRS duration. J Cardiovasc Electrophysiol. 2014;25:500-6.

- 24.Lenarczyk R, Kowalski O, Sredniawa B, Pruszkowska-Skrzep P, Mazurek M, Jędrzejczyk-Patej E, *et al.* Implantation feasibility, procedure-related adverse events and lead performance during 1-year followup in patients undergoing triple-site cardiac resynchronization therapy: A substudy of TRUST CRT randomized trial. J Cardiovasc Electrophysiol. 2012; 23:1228-36.
- 25.Derval N, Bordachar P, Lim HS, Sacher F, Ploux S, Laborderie J, *et al.* Impact of pacing site on QRS duration and its relationship to hemodynamic response in cardiac resynchronization therapy for congestive heart failure. J Cardiovasc Electrophysiol. 2014;25:1012-20.
- 26.Bose A, Kandala J, Upadhyay GA, Riedl L, Ahmado I, Padmanabhan R, *et al.* Impact of myocardial viability and left ventricular lead location on clinical outcome in cardiac resynchronization therapy recipients with ischemic cardiomyopathy. J Cardiovasc Electrophysiol. 2014;25:507-13.
- 27.van Boven N, Bogaard K, Ruiter J, Kimman G, Theuns D, Kardys I, *et al.* Functional response to cardiac resynchronization therapy is associated with improved clinical outcome and absence of appropriate shocks. J Cardiovasc Electrophysiol. 2013; 24:316-22.
- 28.Kandala J, Upadhyay GA, Altman RK, Bose A, Heist EK, Mela T, *et al.* Electrical delay in apically positioned left ventricular leads and clinical outcome after cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2013;24:182-7.
- 29.Gold MR, Leman RB, Wold N, Sturdivant JL, Yu Y. The effect of left ventricular electrical delay on the acute hemodynamic response with cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2014;25:624-30.
- 30.Bogaard MD, Hesselink T, Meine M, Loh P, Hauer RN, Cramer MJ, *et al.* The ECG in cardiac resynchronization therapy: influence of left and right ventricular preactivation and relation to acute response. J Cardiovasc Electrophysiol. 2012;23:1237-45.
- 31.Ploux S, Verdoux H, Whinnett Z, Ritter P, Dos Santos P, Picard F, *et al.* Depression and severe heart failure: Benefits of cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2012;23:631-6.
- 32.Noyes K, Veazie P, Hall WJ, Zhao H, Buttaccio A,

Thevenet-Morrison K, *et al.* Cost-effectiveness of cardiac resynchronization therapy in the MADIT-CRT trial. J Cardiovasc Electrophysiol. 2013;24:66-74.

- 33.Huizar JF, Kaszala K, Koneru JN, Thacker LR, Ellenbogen KA. Comparison of different pacing strategies to minimize phrenic nerve stimulation in cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2013;24:1008-14.
- 34.Rickard J, Cheng A, Spragg D, Cantillon D, Baranowski B, Varma N, *et al*. A clinical prediction rule to identify patients at heightened risk for early demise following cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2014;25:278-82.
- 35.Weinstock J, Estes NA. Cardiac resynchronization therapy: extending current responses to phrenic nerve stimulation. J Cardiovasc Electrophysiol. 2014;25:491-3.
- 36.Ortega M, Merino JL, Blanco FV, Gutiérrez-Larraya F. Cardiac resynchronization therapy in an infant with double outlet right ventricle and mechanical dyssynchrony. J Cardiovasc Electrophysiol. 2012;23: 781-3.
- 37.van Boven N, Theuns D, Bogaard K, Ruiter J, Kimman G, Berman L, *et al*. Atrial fibrillation in cardiac resynchronization therapy with a defibrillator: a risk factor for mortality, appropriate and inappropriate shocks. J Cardiovasc Electrophysiol. 2013;24: 1116-22.
- 38.Stavrakis S, Lazzara R, Thadani U. The benefit of cardiac resynchronization therapy and QRS duration: A meta-analysis. J Cardiovasc Electrophysiol. 2012;23:163-8.
- 39.Dilaveris PE, Gialafos JE. P-wave dispersion: A novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol. 2001;6:159-65.
- 40. Chávez E, Carmona R. Dispersión de la onda P, uso del método manual de medición como recomendación para la práctica médica. Experiencia del Cardiocentro "Ernesto Che Guevara". CorSalud [Internet]. 2011 [citado 30 Ene 2015];3:303-9. Disponible en:

http://www.corsalud.sld.cu/sumario/2011/v3n4a1 1/dispersion.htm

41.Chávez E, González E, Llanes MC, Garí M, García J, Fernández E, et al. Dispersión de la onda P en niños hipertensos, su relación con el peso corporal. Cor-Salud [Internet]. 2012 [citado 30 Ene 2015];4:272-7. Disponible en: http://www.corsalud.sld.cu/sumario/2012/v4n4a1 2/ondap.html

- 42.Varma N. Left ventricular conduction delays and relation to QRS configuration in patients with left ventricular dysfunction. Am J Cardiol. 2009;103: 1578-85.
- 43.Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, *et al*. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013;369:1395-405.
- 44.Dupont M, Rickard J, Baranowski B, Varma N, Dresing T, Gabi A, *et al.* Differential response to cardiac resynchronization therapy and clinical outcomes according to QRS morphology and QRS duration. J Am Coll Cardiol. 2012;60:592-8.
- 45.Guglin M, Curtis. AB. QRS duration criteria to select patients for cardiac resynchronization therapy: Cardiac resynchronization therapy: 150 is not a magic number!. Circ Arrhythm Electrophysiol. 2013;6:429-35.
- 46.Gold MR, Thébault C, Linde C, Abraham WT, Gerritse

B, Ghio S, *et al*. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. Circulation. 2012;126(7):822-9.

- 47.Al Hebaishi YS, Al Shehri HZ, Al Moghairi AM. Predictors of cardiac resynchronization therapy response: The pivotal role of electrocardiogram. ScientificWorldJournal [Internet]. 2013 [citado 05 Feb 2015];2013:837086[aprox. 6 p.]. Disponible en: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC36 15583/pdf/TSWJ2013-837086.pdf
- 48.García-Seara J, Martínez-Sande JL, Cid B, Gude F, Bastos M, Domínguez M, *et al.* Influencia del eje eléctrico QRS preimplante en la respuesta a la terapia de resincronización cardiaca. Rev Esp Cardiol. 2008;61:1245-52.
- 49.Josephson ME, Wellens HJ. The ECG in left bundle branch block and heart failure. Heart Rhythm. 2015;12:250-1.