ORIGINAL ARTICLE

Reverse Electrical Remodeling in Patients Under Cardiac Resynchronization Therapy

Remodelado eléctrico reverso en pacientes tratados con terapia de resincronización cardíaca

JOAQUÍN VÁZQUEZ[1], FEDERICO FERRANDO[1], SOLEDAD MURGUÍA[1], JOSÉ ICHAZO[1], NATALIA ESCOBAR[1], ALEJANDRO CUESTA[1], ÁLVARO RIVARA[1], DIEGO FREIRE[1]

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is indicated in patients who often present cardiac remodeling due to dilatation and contractile dyssynchrony. CRT contributes to reverse remodeling which is associated with reduced mortality and heart failure (HF) hospitalizations. Improvements in intraventricular conduction with decreased ventricular activation time have also been observed. The quantification of reverse electrical remodeling has been underused as a parameter of response, and there are few reports on its association with the clinical-structural response.
Objective: To analyze intraventricular reverse electrical remodeling as a parameter of response to CRT in living individuals.
Methods: We included patients implanted at least 6 months ago. A deactivated stimulation ECG (post-CRT intrinsic QRS, iQRS) was obtained, and by means of transthoracic echocardiography (TTE), the left ventricular ejection fraction (LVEF), the left ventricular end-diastolic diameter (LVEDD) and the presence of mitral regurgitation were defined. Patients were classified according to their clinical-structural response. Electrical remodeling was characterized by comparing pre- and post-CRT QRS duration and assessing QRS changes (ΔiQRS) between groups.
Results: A total of 23 patients were included, 39% of which showed a >10 msec decrease in iQRS. We observed a ΔiQRS of -9.3±20.7 msec in responders, and 11.25±18.9 msec in non-responders (p=0.027), more marked in hyper-responders (ΔiQRS: -14.44±17.40 msec, p=0.026). Women with pre-CRT QRS ≥150 msec showed a significant decrease in iQRS (p=0.0195).
Conclusion: Reverse electrical remodeling was found in 39% of the patients under CRT. We noted a significant relationship between ΔiQRS and clinical-structural response, higher in hyper-responders. Women with wider pre-CRT QRS showed more marked reverse electrical remodeling. This parameter is accessible and easy to read in outpatient visits.

Keywords: Cardiac resynchronization therapy, response, reverse electrical remodeling.

RESUMEN

Introducción: La terapia de resincronización cardíaca (TRC) se indica en pacientes que habitualmente presentan remodelado cardíaco generado por dilatación y disincronía contráctil. La TRC contribuye al remodelado reverso, relacionado con menor mortalidad y hospitalizaciones por insuficiencia cardíaca (IC). Se han observado además mejoras en la conducción intraventricular, con reducción del tiempo de activación. La cuantificación del remodelado eléctrico reverso se ha subutilizado como parámetro de respuesta, con escasos reportes sobre su asociación con la respuesta clínica-estructural.
Objetivo: Analizar el remodelado eléctrico reverso intraventricular como parámetro de respuesta a la TRC.
Material y Métodos: Se incluyeron pacientes con más de 6 meses de implante. Se obtuvo un ECG con estimulación desactivada (QRS intrínseco, QRSi, post-TRC), y por ecocardiograma transtorácico se definió la fracción de eyección ventricular izquierda (FEVI), el diámetro de fin de diástole del ventrículo izquierdo (DFDVI) y la presencia de insuficiencia mitral. Se clasificó a los pacientes según la respuesta clínica-estructural. El remodelado eléctrico se caracterizó con la comparación de la duración del QRS pre-y post-TRC y la valoración de los cambios del QRS (ΔQRSi) entre grupos.
Resultados: Se incluyeron 23 pacientes. Un 39% presentó disminución >10 mseg del QRSi. Observamos un ΔQRSi de -9,3±20,7 mseg en respondedores, y 11,25±18,9 mseg en no respondedores (p=0,027), más acentuada en los hiper respondedores (ΔQRSi: -14,44±17,40 mseg, p=0,026). Las mujeres con QRS ≥150 mseg pre TRC exhibieron disminución significativa del QRSi (p=0,0195).
Conclusiones: El remodelado eléctrico reverso se comprobó en 39% de los pacientes que recibieron TRC. Observamos una relación significativa del ΔQRSi con la respuesta clínica-estructural, mayor en hiper respondedores. Mujeres con QRS ancho pre-TRC exhiben remodelado eléctrico reverso más acentuado. Este es un parámetro de fácil acceso e interpretación durante los controles ambulatorios.

Palabras claves: Terapia de resincronización cardíaca, Respuesta, Remodelado eléctrico reverso.

REV ARGENT CARDIOL 2023;91:37-44. http://dx.doi.org/10.7775/rac.v91.i1.20591

Received: 11/30/2022 – *Accepted:* 12/16/2022

Address for reprints: Joaquín Álvarez. Calle Prudencio Vazquez y Vega 1130bis apto 1001 CP11300. E-mail: joaquin.vazquez.gonzalez@gmail.com

[1] Centro Cardiovascular Universitario Hospital de Clínicas Montevideo

INTRODUCTION

Heart failure (HF) affects 1-2% of the adult population. It has been typically divided into two phenotypes based on the left ventricular ejection fraction (LVEF): HF with slightly reduced or preserved LVEF, and HF with reduced LVEF (HFREF). Cardiac resynchronization therapy (CRT) is mostly indicated for patients with HFREF and major cardiac remodeling, dilated chambers, and impaired ventricular conduction, both closely related to poor prognosis. (1–5)

CRT intends to correct cardiac dyssynchrony by stimulating both ventricles and achieve a more physiological activation and contraction. (6,7) From 25% to 50% individuals with a >120-msec QRS complex have HFREF, and 15-27% experience complete left bundle-branch block (LBBB). (8–10) Maximum benefit has been observed in addition to medical treatment in symptomatic patients with New York Heart Association (NYHA) functional class (FC) II-III, with sinus rhythm and LVEF ≤35%, a QRS longer than 150 msec, and LBBB morphology. (1,2)

This technique has shown the ability to optimize cardiac function and reduce chamber dimensions (reverse remodeling), improve symptoms, anticipate a better condition, and reduce HF hospitalizations and deaths when the patient has been properly screened. (11–15) The degree of reverse remodeling has been directly associated with reduced mortality and hospitalizations. (16–18) To evaluate response (even with heterogeneous definitions), different clinical parameters are used, such as an improved NYHA FC, HF hospitalization rate, and deaths. The most common technique to measure the structural and functional impact is the echocardiography, which is used to estimate the presence and extent of reverse modeling in LV dimensions, generally through end-systolic volume and LVEF improvement. A 15% or higher reduction in ventricular volumes or diameters and at least a 10% increase in LVEF is considered a "positive" response (despite variable cutoff values, according to the registry). The term "hyper-responders" refers to patients with a ≥30% reduction in ventricular volume, or a better systolic function with LVEF >50%. These patients are less likely to be hospitalized because of HF and have a longer survival. (19)

Despite these considerations and multiple technical improvements relative to imaging tests, implantation technique, and availability of more modern and reliable devices, 20% to 40% of patients do not show a favorable response to CRT (non-responders).

This leads to a concern for new and more accurate markers of response, which are easy to access and read. (16,20) The so-called reverse electrical remodeling has been described as another potential tool to measure response to CRT; it leads to reduced QRS, and decreased native (intrinsic) ventricular activation time. (21-23) However, very few reports evaluate its practicality, and there are controversial data on their association with clinical and structural response, though it has been mostly associated with structural remodeling and has even been suggested as a rapid, easy, and low-cost parameter to predict a positive response to CRT. (24-27) Our experience intends to evaluate electrical remodeling as a potential parameter of response in patients under CRT.

OBJECTIVE

To analyze intraventricular reverse electrical remodeling as a parameter of response to CRT in individuals implanted at least 6 months ago.

METHODS

Design

This is an analytical, observational, longitudinal, retrospective, and single-center study.

Population

The study enrolled living patients with chronic HF treated at the Centro Cardiovascular Universitario del Hospital de Clínicas de Montevideo from 2015 to 2021 by implanting a cardiac resynchronizer, with or without an associated defibrillator (CRT-D and CRT-P respectively), within at least 6 months. All patients had permanent complete LBBB at the time of CRT. Complete LBBB was defined according to AHA/ACCF/HRS recommendations. (28) All patients were in NYHA FC II or III at the time of implantation, and a CRT indication based on the guidelines of the European Society of Cardiology. (1,2)

Patients with a pacemaker or with no sinus rhythm at the time of implantation or follow-up, or patients with a resynchronizer implanted as an upgrade to a pacemaker with previous right ventricular stimulation were excluded. Patients with a non-complete LBBB QRS morphology, such as complete right bundle-branch block (RBBB), were also excluded. (1,2) After meeting inclusion and no exclusion criteria, 23 patients were enrolled. Figure 1 shows the study design.

Clinical variables

Clinical data, structural and functional ECGs were collected at the time of implantation based on each patient's medical history and procedure report. In addition, data from outpatient follow-up (Figure 1) were collected, including a brief case history on subjective clinical improvement after CRT, current NYHA FC, and details on the pharmacological treatment.

Device control, records, and surface ECG measures

Based on each patient's medical history, the most recent ECG before the date of CRT implantation was obtained ("pre-CRT" QRS complex, Figure 1). The day when the patient returned for follow-up, the device was followed with programmers. The biventricular stimulation percentage (%BiV) was obtained at the time. There were two new standard 12-lead ECGs per patient, using a FUKUDA DENSHI CARDIMAX FX-2111 electrocardiograph gauged at a 25 mm/s paper speed and with a 0.1 mV/mm voltage. The first ECG was performed with the CRT device stimulated according to usual patient programming (stimulated QRS). To assess intrinsic ventricular activation ("post-CRT" iQRS), a second ECG was performed 5 minutes after temporary implantation discontinuation, programming the device as an off (ODO) or on-demand (VVI) CRT with a HR of 40 bpm.

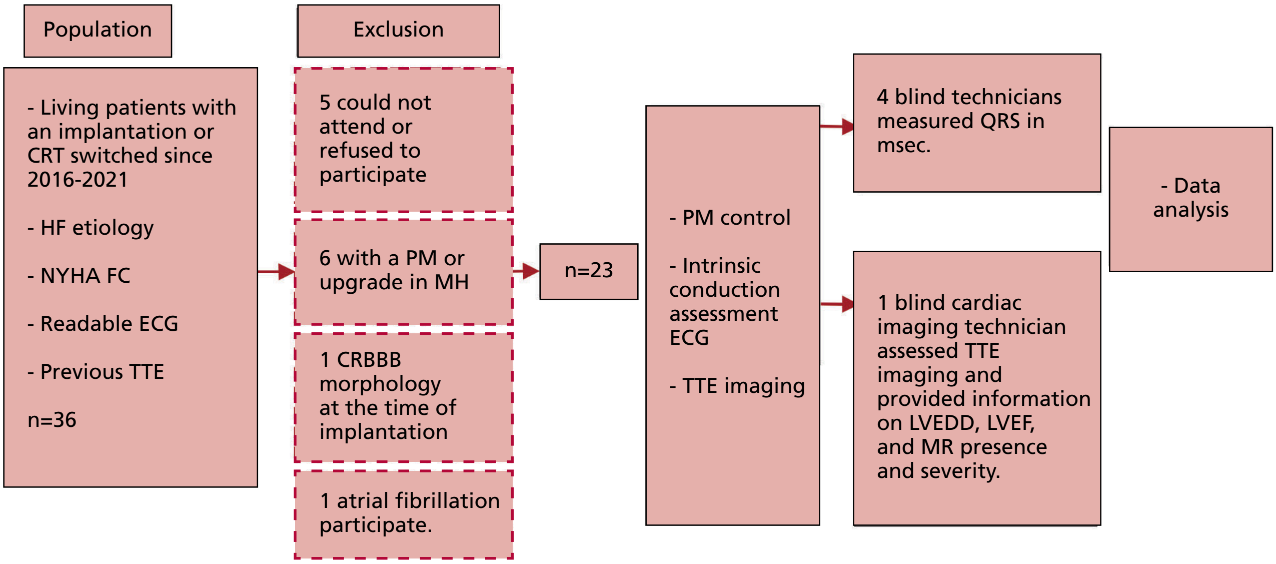

Fig. 1. Study design. CRBB: complete right bundle block. CRT: cardiac resynchronization therapy. ECG: electrocardiogram HF: heart failure. LVEDD: left ventricular end-diastolic diameter. LVEF: left ventricular ejection fraction. MH: medical history. MR: mitral regurgitation. NYHA: New York Heart Association. PM: pacemaker. TTE: transthoracic echocardiography

After recording, the device was reprogrammed with the patient's previous setup.

These ECG showed presence or absence of sinus rhythm. Three electrophysiologists and one electrophysiology-trained cardiologist were asked to measure the duration of QRS complexes (msec) with the most representative leads, concealing any data that might identify the patients and ensuring that those measuring QRS complexes ignored CRT response.

Structural variables (TTE)

The transthoracic echocardiography (TTE) report closest to, and before the date of CRT implantation was obtained from the patient's previous medical history. These reports showed pre-CRT LVEF data, the left ventricular end-diastolic diameter (pre-CRT LVEDD), and the presence and extent of mitral valve regurgitation (pre-CRT MR).

On the day of the new ECG, and after checking the device, each patient had a new TTE performed using ultrasound General Electric Vivid iQ equipment with a 3.5 Mhz transducer, as recommended by the American Society of Echocardiography. Images of two and four chambers apical and left parasternal areas were captured using color Doppler. An echocardiography technician, also blind to clinical data, read the images, estimated the LVEF using the biplane Simpson method (post-CRT LVEF), measured the LVEDD, and defined the presence and severity of mitral regurgitation (post-CRT MR).

CRT response definition

The patient was categorized as a "clinical responder" and/or "structural responder" based on the most common criteria to evaluate response to CRT (13,16,29–31):

- A "clinical responder" is someone with subjective improvement and at least one level improvement (reduction) in the NYHA functional class as compared to the value before the implantation.
- A "structural responder" is someone with reduced LV diameters by at least 15% and/or increased LVEF by at least 10%.
- A "hyper-responder" is someone with reduced LV diameters by 30% and/or normal LVEF.

Statistical analysis

Normal data distribution was checked using the Anderson-Darling normality test. Continuous variables are presented as mean ± standard deviation (SD), or median and interquartile range (IQR) of 25-75%, as appropriate. Categorical variables are presented with absolute and relative frequencies. To evaluate changes in the continuous variable of interest, iQRS, in response to CRT (pre/post CRT analysis), the t test or Wilcoxon test for paired data was used, as appropriate. Also, behavior of ΔiQRS as a continuous variable (post-CRT QRS – pre-CRT QRS in msec) was compared in responders vs. non-responders (paired t test or Mann-Whitney test, as appropriate). These analyses were performed for the clinical-structural (CS) response and hyper-response across the sample and certain subgroups of patients (female vs. male, baseline QRS >150 msec vs. <150 msec, females with a baseline QRS >150 msec vs QRS <150 msec, patients with vs without improved MR). A p-value <0.05 was considered statistically significant. All graphical analyses used software Graph Pad Prism, version 9.0.

Ethical considerations

The ethical principles set forth in the Declaration of Helsinki and latest amendments for research in humans were followed. All patients were called to be informed about the study prior to enrollment. At the time of evaluation in the clinic, each patient gave their written informed consent. The study and informed consent provided to the patients had been previously approved by the Hospital de Clínicas Ethics Committee.

Table 1. Baseline study population characteristics (pre-CRT)

Clinical variables	
Female, n (%)	12 (52)
Age at the time of implantation (years), mean+SD	60±12
Time since implantation (months), mean+SD	43±20
Non-ischemic etiology (n, %)	19 (82)
Medications, n (%)	
o ACEi/ARB	20 (86)
o BB	23 (100)
o MRA	18 (78)
o OMT	17 (73)
Pre-CRT NYHA FC, n (%)	
o II	9 (39)
o III	14 (61)
Echocardiographic variables	
LVEF (%) mean+SD	26.3±5.7
LVEDD (mm), mean+SD	66.6±12.7
At least moderate MR, n (%)	10 (43)
ECG variables	
Duration of intrinsic QRS (msec), median (IQR 25-75)	160 (150-170)
Duration of stimulated QRS (msec), mean+SD	119±19
BiV implantation (%), median (IQR 25-75)	99 (95-100)

ACEi: angiotensin-converting enzyme inhibitors. ARB: angiotensin II receptor blockers. BB: beta-blockers. BiV: bi ventricular. CRT: cardiac resynchronization therapy. IQR: interquartile range. LVEDD: left ventricular end-diastolic diameter. LVEF: left ventricular ejection fraction. MR: mitral regurgitation. MRA: mineralocorticoid receptor antagonists. NYHA FC: New York Heart Association functional class. OMT: optimal medical therapy. SD: standard deviation.

RESULTS

Study population characteristics

A total number of 23 patients were enrolled. Clinical, echocardiographic, implant-related, and electrocardiographic variables are displayed in Table 1.

The patients across the sample showed a similar per-sex distribution; 12 were female (52%). Four (18%) patients had ischemic heart disease, and 19 (82%) patients had non-ischemic heart disease. The average age at the time of implantation was 60±12 years, while the age at the time of follow-up was 64±12 years. The mean follow-up from implantation to control was 43±20 months, ranging from 7 to 96 months.

A high rate of treatment adherence was observed among patients; 73% were under simultaneous therapy with beta-blocker (BB), angiotensin converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB)/sacubitril-valsartan, and mineralocorticoid receptor antagonists (MRA). All patients were receiving BB at the time of follow-up.

The duration of the intrinsic QRS complex prior to CRT was 160 (150-170) msec, and after the CRT, it was 160 (140-160) msec. Nine (39%) patients showed at least a 10 msec reduction in the iQRS duration. Maximum reduction was 40 msec and occurred in three patients. The iQRS increased in eight patients and remained stable in six.

Analysis of response to CRT

Table 2 shows the characteristics of CRT responders. Twenty-one (91%) patients in our study were "clinical responders". The ΔiQRS in this group was -4.7±20.4 msec. Structurally and functionally, both LVEDD and increased LVEF showed enhanced response to CRT during follow-up. LVEDD decreased from 66.6±12.7

Table 2. ECG and clinical response to CRT (pre- and post-CRT analysis)

Response parameters	Pre-CRT	Post-CRT	p-value
Structural variables			
LVEF (%) mean+SD	26.3±5.7	41.6±13.4	<0.0001
LVEDD (mm), mean+SD	66.6±12.7	61.7±12.9	<0.0001
ECG variables			
QRS (msec), median (IQR 25-75)	160 (150-170)	160 (140-160)	0.63

CRT: cardiac resynchronization therapy. LVEDD: left ventricular end-diastolic diameter. LVEF: left ventricular ejection fraction;

mm pre-CRT to 61.7±12.9 mm post-CRT, with a higher than 15% reduction in 7 patients (30.4%). LVEF increased from 26.3±5.7% to 41.6±13.4%, with a higher than 10% increase in 16 patients (70%).

Fifteen (65%) patients were considered "responders" based on both structural and clinical criteria. The LVEDD was significantly reduced from 64.6±8.7 mm to 59.8±7.5 mm, and the LVEF increased from a baseline value of 25.5±6.8% to 40.6±9.5% (Table 2). Nine (39%) patients were "hyper-responders". All of them had clinical response.

As shown in Table 2, the pre- and post-CRT analysis of the total number of patients found that the duration of QRS did not vary significantly following the CRT.

Figure 2 shows a sample case, with iQRS measurements before and after the CRT in a "responder".

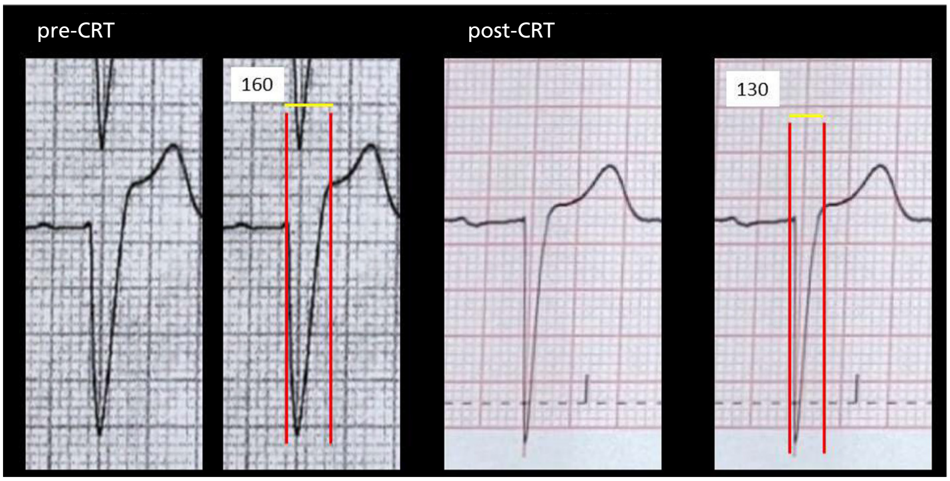

Fig. 2. Reverse electrical remodeling of the left ventricle before and after CRT. (Images are repeated using calipers and measures.) This patient showed increased LVEF from 28% to 52%, and decreased LVEDD from 77 to 58 mm.
CRT: cardiac resynchronization therapy

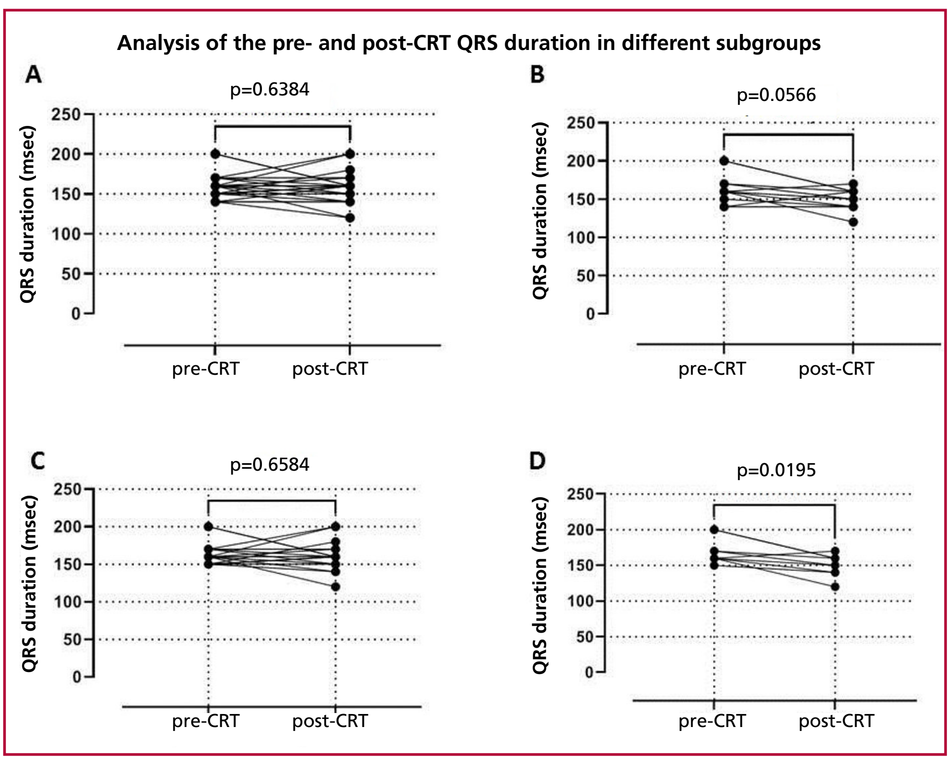

Fig. 3. Differences in iQRS before and after the CRT in the entire population (A), the female subgroup (B), individuals with an initial QRS ≥150 msec (C), and women with an initial QRS ≥150 msec (D).
CRT: cardiac resynchronization therapy

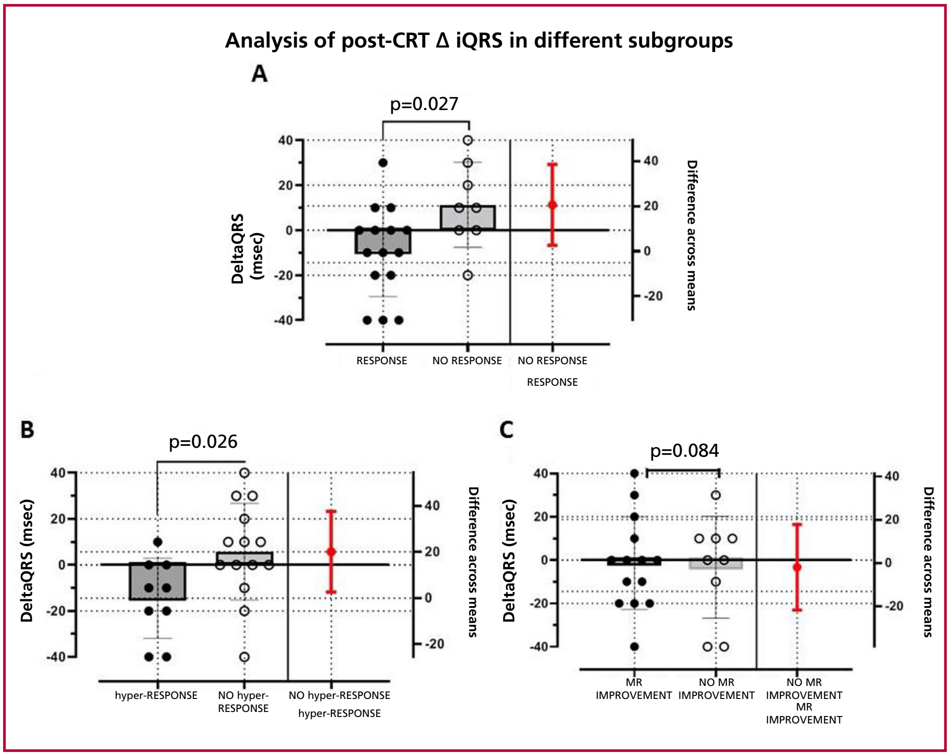

Fig. 4. ΔiQRS charts are shown by subgroups. A: Clinical-structural response to CRT (p=0.027); B: Hyper-responders; C: Mitral regurgitation improvement.
CRT: cardiac resynchronization therapy

Subgroup analysis

There was a trend in iQRS duration variation after the CRT in the female subgroup, though it lacked statistical significance (p=0.056, Figure 3B). Changes in the duration of iQRS were not higher in those with a baseline QRS of ≥150 msec (p=0.65, Figure 3C). Upon analysis of the subgroup of women with an initial QRS ≥150 msec prior to CRT, significant reduction of the iQRS was observed (p=0.0195, Figure 3D).

The change in pre- and post-CRT iQRS duration was unrelated to the non-ischemic etiology (p=0.72) or to age (p=0.78).

The ΔiQRS was -9.3±20.7 msec among clinical-structural "responders," and 11.25±18.9 msec among non-responders (p=0.027). This difference was slightly larger among "hyper-responders," with a ΔiQRS of -14.44±17.40 msec (p=0.026). There was no significant association of ΔiQRS with MR improvement (p=0.84). (Figure 4)

DISCUSSION

To the best of our knowledge, this is the first study to describe reverse electrical remodeling in patients under local and regional CRT.

After CRT, the duration of iQRS was reduced at least 10 msec in nine of the patients, though this lacked statistical significance. In observational studies like ours, QRS reduction was significant and generally associated with increased LVEF. (21) Subgroup analysis shows that ΔiQRS is related to clinical-structural response, more markedly in patients having a "hyper-response" to CRT. Despite sample size limitations, our findings contribute to the hypothesis that a shorter QRS leads to an improved intraventricular conduction system, and therefore, reverse LV remodeling. Further investigation is required to assess this hypothesis.

We showed a tendency towards stronger electrical remodeling in women with a wider baseline QRS. This is consistent with traditional response definitions. (1, 31-33)

Mechanisms resulting in reverse electrical remodeling are not fully known. It might be said that improvements in the size of chambers favor faster conduction upon myocardium contraction. It has also been suggested that this may happen as a result of full or partial recovery of the specialized conduction system itself. (22, 33,34) Another possible CRT-related effect is reduced cardiac fibrosis. (35) The underlying question also involves pathophysiological complete LBBB mechanisms and their multiple physiological and anatomical variants, an electrocardiographic pattern that may lead to completely interrupted or delayed conduction across the left bundle branch, which might result in right bundle branch overexpression. (36)

The cutoff point used to define electrical remodeling is even less consistent. Sebag et al. prospectively enrolled 85 patients with CRT indication, and evaluated clinical, echocardiographic, and electrocardiographic variables before and 12 months after the CRT. They found 19 and 18 msec cutoff points, with a sensitivity and specificity of 86/60% and 84/60%, respectively, to associate ΔiQRS with the clinical and echocardiographic response, respectively. Following a multivariate analysis, ΔiQRS ≥20 msec was an independent predictor of the echocardiographic response. (26)

We showed a tendency towards a reduced native QRS relative to improved MR, reaching no significance. The study by Karaca et al. found that reverse electrical remodeling is associated with improved MR and geometry of the mitral valve anatomy. (34) According to them, in addition to secondary improvement thanks to the cited ventricular remodeling, reversed papillary muscles dyssynchrony may lead to a major CRT-related benefit, and both clinical and functional enhancement.

Future prospective investigations are required to assess the clinical, structural and electrical response in several specific subpopulations of patients undergoing CRT, in an attempt to better understand the pathophysiology of its effects. We consider this becomes more relevant and that it will merit new studies to know if the reverse electric remodeling is similar or more accentuated in the era of stimulationof the specific conduction system. (37, 38)

Conflicts of interest

None declared.

(See authors conflicts of interest forms in the website/ Supplementary material)

REFERENCES

1. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Vol. 42, European Heart Journal. Oxford University Press; 2021. p. 3427–520.

2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. Corrigendum to: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2021 Dec 21;42(48):4901–4901.

3. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007 Sep;93(9):1137–46.

4. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. Am J Med. 2009 Nov;122(11):1023–8.

5. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet. 2018;391(10120):572–80.

6. Leclercq C, Hare JM. Ventricular resynchronization: current state of the art. Circulation. 2004 Jan 27;109(3):296–9.

7. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. J Am Coll Cardiol. 2002 Jan 16;39(2):194–201.

8. Olshansky B, Day JD, Sullivan RM, Yong P, Galle E, Steinberg JS. Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION Trial. Heart Rhythm. 2012 Jan;9(1):34–9.

9. Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjaer H, Johannessen A, et al. Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. Eur J Heart Fail. 2009 Jul;11(7):699–705.

10. Friedman DJ, Bao H, Spatz ES, Curtis JP, Daubert JP, Al-Khatib SM. Association Between a Prolonged PR Interval and Outcomes of Cardiac Resynchronization Therapy: A Report From the National Cardiovascular Data Registry. Circulation. 2016 Nov 22;134(21):1617–28.

11. Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005 Apr 14;352(15):1539–49.

12. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, de Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004 May 20;350(21):2140–50.

13. 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 Dec 2;52(23):1834–43.

14. 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 Oct 1;361(14):1329–38.

15. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure. New England Journal of Medicine. 2010 Dec 16;363(25):2385–95.

16. Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: Implant and follow-up recommendations and management. Heart Rhythm. 2012;9(9):1524–76.

17. Solomon SD, Foster E, Bourgoun M, Shah A, Viloria E, Brown MW, et al. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. Circulation. 2010 Sep 7;122(10):985–92.

18. Ypenburg C, van Bommel RJ, Borleffs CJW, Bleeker GB, Boersma E, Schalij MJ, et al. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. J Am Coll Cardiol. 2009 Feb 10;53(6):483–90.

19. Steffel J, Ruschitzka F. Superresponse to cardiac resynchronization therapy. Circulation. 2014 Jul 1;130(1):87–90.

20. Ellenbogen KA, Wilkoff BL, Kay GN, Lau CP, Auricchio A. Clinical Cardiac Pacing, Defibrillation and Resynchronization therapy. Fifth. ELSEVIER; 2017. 490–522 p.

21. Henrikson CA, Spragg DD, Cheng A, Capps M, Devaughn K, Marine JE, et al. Evidence for Electrical Remodeling of the Native Conduction System with Cardiac Resynchronization Therapy.

22. Dizon J, Horn E, Neglia , John, Medina N, Garan H. Loss of Left Bundle Branch Block following Biventricular Pacing Therapy for Heart Failure: Evidence for Electrical Remodeling? Journal of Interventional Cardiac Electrophysiology. 2004 Feb;10(1):47–50.

23. Qian Z, Qin C, Zou F, Xue S, Wang Y, Zhang X, et al. Complete electrical reverse remodeling of native conduction after resynchronization therapies. Int J Cardiol. 2022 Jun 15;357:81–7.

24. Stockburger M, Nitardy A, Fateh-Moghadam S, Krebs A, Celebi O, Karhausen T, et al. Electrical Remodeling and Cardiac Dimensions in Patients Treated by Cardiac Resynchronization and Heart Failure Controls.

25. Mischke K, Knackstedt C, Fache K, Reith S, Rana O, Saygili E, et al. Electrical remodelling in cardiac resynchronization therapy: decrease in intrinsic QRS duration. Acta Cardiologica. 2011 Apr;66(2):175–80.

26. 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. Journal of Cardiovascular Electrophysiology. 2012 Nov;23(11):1219–27.

27. Tereshchenko LG, Henrikson CA, Stempniewicz P, Han L, Berger RD. Antiarrhythmic effect of reverse electrical remodeling associated with cardiac resynchronization therapy. PACE - Pacing and Clinical Electrophysiology. 2011 Mar;34(3):357–64.

28. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation. 2009 Mar 17;119(10):e235-40.

29. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, et al. Predictors of Super-Response to Cardiac Resynchronization Therapy and Associated Improvement in Clinical Outcome. J Am Coll Cardiol. 2012 Jun;59(25):2366–73.

30. Gold MR, Rickard J, Daubert JC, Zimmerman P, Linde C. Redefining the Classifications of Response to Cardiac Resynchronization Therapy: Results From the REVERSE Study. JACC: Clinical Electrophysiology. 2021 Jul 1;7(7):871–80.

31. Goldenberg I, Moss AJ, Hall WJ, Foster E, Goldberger JJ, Santucci P, et al. Predictors of Response to Cardiac Resynchronization Therapy in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT). Circulation. 2011 Oct 4;124(14):1527–36.

32. Saxon LA, Bristow MR, Boehmer J, Krueger S, Kass DA, de Marco T, et al. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. Circulation 2006;114:2766-72. https://doi.org/10.1161/CIRCULATIONAHA.106.642892
33. Yang XW, Hua W, Wang J, Liu ZM, Ding LG, Chen KP, et al. Native QRS narrowing reflects electrical reversal and associates with anatomical reversal in cardiac resynchronization therapy. Journal of Interventional Cardiac Electrophysiology 2014;41:161–8. https://doi.org/10.1007/s10840-014-9936-5
34. Karaca O, Cakal B, Omaygenc MO, Gunes HM, Cakal SD, Kizilirmak F, et al. Native Electrocardiographic QRS Duration after Cardiac Resynchronization Therapy: The Impact on Clinical Outcomes and Prognosis. J Cardiac Fail 2016;22:772–80. https://doi.org/10.1016/j. cardfail.2016.04.001
35. Sunman H, Canpolat U, Yorgun H, Ozkan A, Yalçn MU, Bayrak T, et al. Association between reverse electrical remodeling and cardiac fibrosis markers in patients with cardiac resynchronization therapy. Turk Kardiyoloji Dernegi Arsivi 2018;46:84-91. https://doi.org/10.5543/tkda.2017.80236
36. Tan NY, Witt CM, Oh JK, Cha YM. Left Bundle Branch Block: Current and Future Perspectives. Circulation: Arrhythmia and Electrophysiology. Lippincott Williams and Wilkins; 2020. p. 364–77. https://doi.org/10.1161/CIRCEP.119.008239
37. Ponnusamy SS, Arora V, Namboodiri N, Kumar V, Kapoor A, Vijayaraman P. Left bundle branch pacing: A comprehensive review. J Cardiovasc Electrophysiol. 2020;31:2462-73.
38. Vijayaraman P, Chung MK, Dandamudi G, Upadhyay GA, Krishnan K, Crossley G, et al. His Bundle Pacing. J Am Coll Cardiol 2018;72:927-47. https://doi.org/10.1016/j.jacc.2018.06.017