



Echocardiographic and electrocardiographic factors associated with non-response to cardiac resynchronization therapy

Factores ecocardiográficos y electrocardiográficos asociados con la no respuesta a la terapia de resincronización cardíaca

Araceli Villanueva-Balandrán,* Oswaldo Aldana-Varela,* Marco Antonio Hernández-Mercado†

Keywords:

cardiac
resynchronization
therapy, heart failure,
fragmented QRS,
dilated left ventricle.

Palabras clave:

terapia de
resincronización
cardíaca, insuficiencia
cardíaca, QRS
fragmentado,
ventrículo izquierdo
dilatado.

* Resident Doctor
of the Cardiology
and Cardiovascular
Surgery Service of the
Toluca Medical Center,
ISSEMyM, «Lic. Arturo
Montiel Rojas». State
of México, México.

† Cardiologist. Head
of the Cardiology and
Cardiovascular Surgery
Department of the
Toluca Medical Center,
ISSEMyM, «Lic. Arturo
Montiel Rojas». State
of Mexico, Mexico.

Received:
08/21/2022

Accepted:
10/26/2022

ABSTRACT

Introduction: Heart Failure (HF) is a public health problem in Mexico and worldwide. It is one of the most frequent causes of hospitalization and death in the cardiology and internal medicine departments. Cardiac Resynchronization Therapy (CRT) has been an effective treatment for selected patients with HF. However, even in patients with class I recommendations, the rate of non-response is up to 30%, which makes it necessary to identify predictors of non-response. **Objective:** to find predictors of non-response to CRT. **Material and methods:** the electrocardiographic and echocardiographic features of patients who received CRT at ISSEMyM Medical Center of Toluca (IMCT) were analyzed between June 1st 2003, and June 1st 2019. We looked for an association between these features and the response or non-response to CRT one year after the implantation. A sample of 24 patients with a class I recommendation for CRT were studied; a Multivariate logistic regression analysis was performed to identify predictors of non-response. **Results:** 62.5% of the patients with a Left Ventricle End-Diastolic Diameter (LVEDD) ≥ 77 mm were non-responders ($p = 0.003$); 75% of the patients with fragmented QRS in the electrocardiogram previous to the CRT were non-responders, although this last result with a non-statistically significant p (0.083). **Conclusions:** the LVEDD ≥ 77 strongly predicts non-response to CRT. As for the fragmented QRS pattern, even when 75% of patients had it were non-responders, a bigger sample might be required to find statistical significance.

RESUMEN

Introducción: la Insuficiencia Cardíaca (IC) es un problema de salud pública en México y a nivel mundial, es una de las causas más frecuentes de hospitalización y de muerte en los servicios de cardiología y medicina interna. La Terapia de Resincronización Cardíaca (TRC) ha sido un tratamiento efectivo en pacientes seleccionados con IC. Sin embargo, aun en los pacientes con recomendación clase I, la tasa de no respondedores es de hasta 30%, por lo que es necesario identificar predictores de no respuesta. **Objetivos:** encontrar predictores de no respuesta a la terapia de resincronización cardíaca. **Material y métodos:** se revisaron las características electrocardiográficas y ecocardiográficas en pacientes que recibieron TRC en el Centro Médico ISSEMyM Toluca entre el 1º de junio de 2003 y el 1º de junio de 2019. Se buscó la asociación entre estos factores y la respuesta o no respuesta a un año del implante. Se analizó una muestra de 24 pacientes con recomendación clase I para TRC. Se utilizó análisis de regresión logística multivariable para identificar predictores de no respuesta. **Resultados:** el 62.5% de los pacientes que tenían un Diámetro Telediastólico del Ventrículo Izquierdo (DTVI) ≥ 77 mm fueron no respondedores ($p = 0.003$); 75% de los pacientes con patrón fragmentado del QRS en el electrocardiograma fueron no respondedores, aunque este último resultado tuvo una p estadísticamente no significativa (0.083). **Conclusiones:** el DTVI ≥ 77 mm es un fuerte predictor de no respuesta a la TRC. En cuanto al patrón fragmentado del QRS, a pesar de que 75% no respondió, podría ser necesaria una muestra de pacientes más grande para encontrar significancia estadística.

How to cite: Villanueva-Balandrán A, Aldana-Varela O, Hernández-Mercado MA. Echocardiographic and electrocardiographic factors associated with non-response to cardiac resynchronization therapy. Cardiovasc Metab Sci. 2023; 34 (1): 8-12. <https://dx.doi.org/10.35366/110246>

INTRODUCTION

Hear^t Failure (HF) is a public health problem with a high mortality rate. A recent United States of America (USA) study found that the deaths caused by HF had increased from 275,000 in 2009 to 310,000 in 2014.¹ In Europe, the incidence of HF is 3/1,000 people per year (all age groups) or 5/1,000 people per year in adults.^{2,3} The treatment for HF is costly for any country. In the USA, the annual cost of HF in 2010 was estimated at \$39.2 billion, corresponding to 2% of the total US healthcare budget.⁴ A revision from different European countries found similar HF-related costs for overall health care expenditure.^{5,6} Not many studies have evaluated the incidence of HF in Latin America. Ciapponi et al.⁷ report an incidence of 199 cases per 100,000 person-years, a prevalence of 1%, and a 1-year mortality rate of 24.5%; for these reasons, it is imperative to optimize HF management. Cardiac Resynchronization Therapy (CRT) reduces morbidity and mortality in selected patients⁸ and improves cardiac function and quality of life.^{9,10} The currently approved class IA indication for CRT is in patients with optimal drug therapy who are still symptomatic and have Left Ventricle Ejection Fraction (LVEF) < 35%, QRS width > 150 ms and QRS morphology of Left Bundle Branch Block (LBBB).¹¹ Despite implementing CRT in patients with class I recommendation, the rate of non-response is up to 30%.¹²⁻¹⁴ Although, studies have shown that response rates range from 32 to 91%, depending on the criteria used to define response.¹⁵ The definitions adopted in randomized essays versus clinical practice remain discrepant. Clinical essays typically measure variables based on events, while less defined criteria are used in practice. Various definitions of CRT response have been proposed, and the response rate is different in every case.^{15,16} Response rates are higher when clinical parameters such as symptoms are used but much lower when using outcome measures or ventricular remodeling.¹² For this study, the definition by Hu YR et al.¹⁷ was used, in which after one year of follow-up, patients were defined as non-responders if the LVEF increased $24.5 \pm 3.7\%$

vs $26.2 \pm 4.0\%$ or less with a reduction of the Left Ventricle End-Diastolic Diameter (LVEDD) of $76.8 \pm 6.3\%$ vs $75.3 \pm 7.3\%$. Patients were classified as responders if their LVEF increased by $27.4 \pm 5.2\%$ vs $42.5 \pm 10.4\%$ or more and had a reduction of the LVEDD of 70.3 ± 9.1 vs 61.8 ± 10.3 mm or greater. Many parameters have been used to predict non-response to CRT, such as electrocardiographic, echocardiographic and clinical parameters. Hu YR et al,¹⁷ after much logistic regression analysis, found that two variables were strongly associated with non-response to CRT after one year of follow-up: fragmented QRS and LVEDD ≥ 77 mm. If any of the two was present, the probability of non-response was 14-17%; if both variables were present, the probability of non-response was close to 50%. For this study, electrocardiographic and echocardiographic features pre-CRT and their association with non-response to the therapy were analyzed.

MATERIAL AND METHODS

A retrospective and observational study was performed with patients from the cardiology department of the ISSEMyM Medical Center of Toluca (IMCT), who were treated with CRT with or without an Implantable Cardioverter Defibrillator (ICD) from June 1st, 2003, to June 1st, 2019. A sample of 24 patients was used. The inclusion criteria were 18 years old or older, both genders and having received CRT. Exclusion criteria were a basal QRS length of less than 120 ms and patients with LVEF of 40% or greater before the procedure. The only elimination criterion was death before the control echocardiogram post-CRT. The electrocardiographic features analyzed were the length of the QRS, the presence of LBBB and the presence of a fragmented QRS complex previous to the CRT. The echocardiographic feature was the end-diastolic diameter of the left ventricle previous to the CRT. A descriptive statistics analysis was performed using normality and symmetry tests for the quantitative variables. The minimum, maximum, median and standard deviation were calculated, with a 95% confidence interval for the median. For the qualitative variables, we obtained absolute and relative frequencies; cross-tabulation

for variables association. Inferential statistics consisted of applying Pearson's χ^2 test, the one-factor ANOVA test and Wilcoxon's test, all with a p-value < 0.05. The database was organized in excel, and we used the SPSS program 22 version for the analysis.

RESULTS

A total of 24 patients were included, two were excluded, and two were eliminated. The average age was 65.8 ± 12.0 years, with a minimum of 38 years and a maximum of 88 years. Sixteen patients were classified as responders, and eight patients as non-

responders. When comparing age among groups, no statistically significant differences were found. The distribution by gender mainly corresponded to males, with 79% (19 cases). When comparing gender among groups, no statistically significant association was found. However, it is worth noting that 100% of the females were responders, vs 57.9% of males, with an Odds Ratio (OR) of 1.7 times for the female gender. Previous LBBB was associated with response to CRT with statistical significance, with a protection odds ratio of 0.722 times. We found that 75% of the patients with a fragmented QRS complex were non-responders to CRT (Table 1).

Figure 1 shows a comparison between pre-LVEDD and post-LVEDD. The investigators found that patients with the highest values of LVEDD pre-CRT, with a mean of 77 mm, were classified as non-responders, vs a mean value of 63 mm for patients classified as responders.

Figure 2 shows a comparison of the frequency of the different variables and their association with the response or non-response to CRT. It is noticeable that the percentage of responders was greater in patients without a fragmented QRS pattern in their electrocardiogram, with a previous LVEDD smaller than 77 mm and a QRS length equal to or greater than 150 ms, though only the LVEDD < 77 mm previous to CRT was statistically significant.

In counterpart, Figure 3 shows the association between the variables and non-responders. It is evident that the variable that had a greater association with non-response to CRT was the fragmented QRS pattern, with 75%, though without statistical significance. 62.5% of patients with an LVEDD of 77 mm or greater were classified as non-responders, with statistical significance. The length of the QRS < 150 ms was present in 37.5% of non-responders without statistical significance.

DISCUSSION

Many trials have found electrocardiographic features associated with response to CRT, such as the length of the QRS > 150 ms and the presence of LBBB.^{18,19} Moreover, they have also used echocardiographic parameters like the LVEF, LVEDD and the Left Ventricular End-

Table 1: Association between a fragmented QRS complex and response to Cardiac Resynchronization Therapy.

Fragmented QRS complex	Responder		Total
	Yes n (%)	No n (%)	
Yes	6 (37.5)	6 (75.0)	12 (50.0)
No	10 (62.5)	2 (25.0)	12 (50.0)
Total	16 (100.0)	8 (100.0)	24 (100.0)

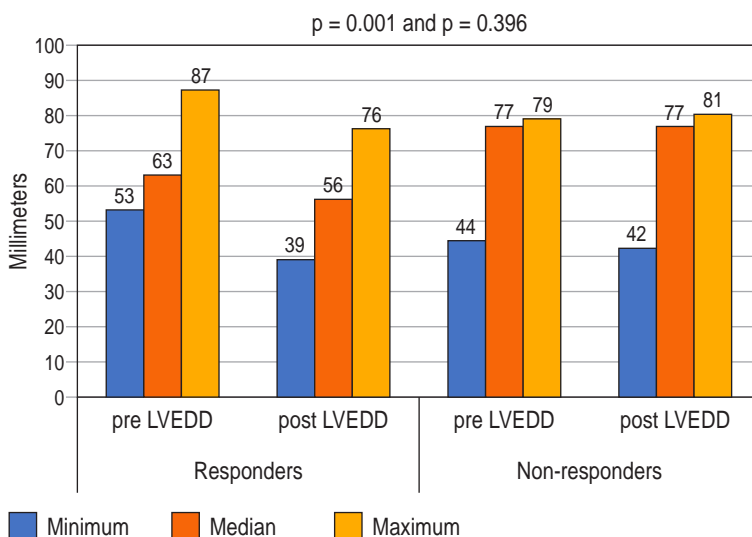


Figure 1: Comparison of pre and post-LVEDD between groups. LVEDD = Left Ventricle End-Diastolic Diameter.

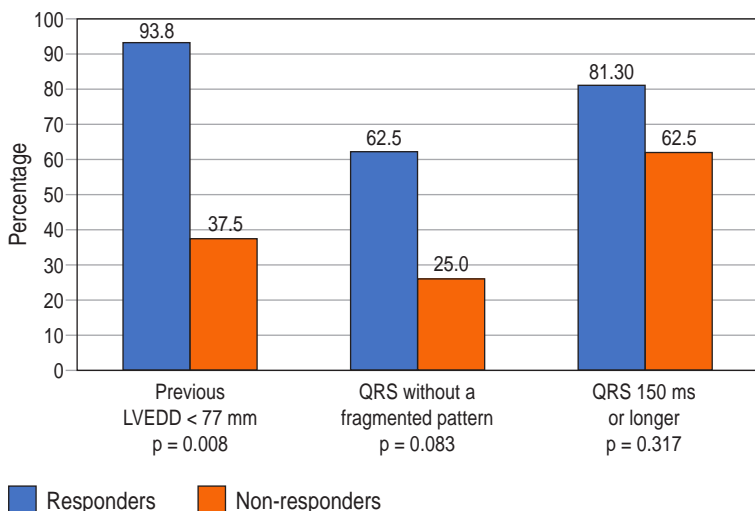


Figure 2: Frequency of responders vs non-responders and variables of the study. LVEDD = Left Ventricle End-Diastolic Diameter.

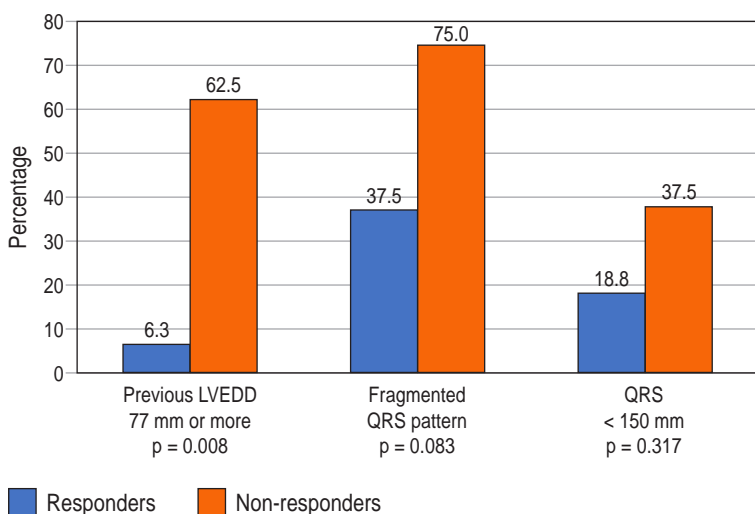


Figure 3: Variables association with non-responders. LVEDD = Left Ventricle End-Diastolic Diameter.

Systolic Volume Index (LVESVI) to determine the positive response to CRT.^{18,19} However, very few studies have been designed to find predictors of non-response. After a comprehensive revision of the literature, we found only two trials designed that way.^{17,20} Hu YR et al.¹⁷ found that the presence of a fragmented QRS and a dilated LVEDD prior to CRT are strong predictors of non-response. In patients with both features, the

rate of non-response was 46.2%. Shanks M et al.²⁰ concluded that patients with a shorter QRS duration (150.6 ± 29.9 milliseconds vs 156.0 ± 32.5 milliseconds, $p = 0.041$) and larger left atrial volumes (44.9 ± 16.9 mL/m² vs 40.9 ± 17.6 mL/m², $p = 0.006$) were more frequently non-responders. In the present study, we found that most patients with QRS length < 150 ms were non-responders, with a p-value of 0.317. The atrial volumes were also determined, but there was no association with response to CRT. Similar to the results obtained by Hu YR et al.,¹⁷ we found that two parameters were associated with non-response to CRT, an LVEDD > 77 mm and a fragmented QRS pattern. Nevertheless, only the first one had a significant p-value. The main limitation of this study was the small sample size, it is likely that if the number of patients is increased, we might obtain more statistically significant results.

CONCLUSIONS

The LVEDD greater than 77 mm prior to the cardiac resynchronization therapy is a strong predictor of non-response. The fragmented QRS pattern previous to CRT was associated with non-response, although with a p-value > 0.05. It is necessary to do studies with much bigger sample sizes to increase these findings' statistical significance.

Funding/support: no financial support was received for this study.

Conflict of interest: the authors declare no conflict of interests.

REFERENCES

1. Ni H, Xu J. Recent trends in heart failure-related mortality: United States, 2000-2014. NCHS Data Brief; 2015, 1.8.
2. Meyer S, Brouwers FP, VoonsAA, Hillege HL, de Boer RA, Gansevoort RT et al. Sex differences in new-onset heart failure. Clin Res Cardiol. 2015; 104: 342-350.
3. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort 11-year follow-up of PREVEND. Eur Heart J. 2013; 34: 1424-1431.
4. Lloyd-Jones D, Adamas RJ, Brown TM, Carnethon M, Dai S, De Simone G et al. Heart disease and

- stroke statistics - 2010 update: a report from the American Heart Association *Circulation* 2010; 121: e46-215.
5. Liao L, Allen LA, Whellan DJ. Economic burden of heart failure in the elderly. *Pharmacoeconomics*. 2008; 26: 447-462.
 6. National Clinical Guideline Centre. The management of chronic heart failure in adults in primary and secondary care, 2010. Available in: <http://guidance.nice.org.uk/CG108/Guidance/pdf/English>
 7. Ciapponi A, Alcaraz A, Calderón M, Matta MG, Chaparro M, Soto N et al. Burden of heart failure in Latin America: a systematic review and meta-analysis. *Rev Esp Cardiol (Engl Ed)*. 2016; 69 (11): 1051-1060.
 8. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J*. 2013; 34: 3547-3556.
 9. Cleland JG, Freemantle N, Erdmann E, Gras D, Kappenberger L, Tavazzi L et al. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. *Eur J Heart Fail*. 2012; 14: 628-634.
 10. Sohaib SM, Finegold JA, Nijjer SS, Hossain R, Linde C, Levy WC et al. Opportunity to increase life span in narrow QRS cardiac resynchronization therapy recipients by deactivating ventricular pacing: evidence from randomized controlled trials. *JACC Heart Fail*. 2015; 3: 327-336.
 11. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) with the special contribution of the European Heart Rhythm Association (EHRA) [Internet]. OUP Academic. Oxford University Press; 2021 [cited 2022 Jul 31]. Available in: <https://doi.org/10.1093/eurheartj/ehab364>
 12. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. *Eur Heart J* 2017; 38 (19): 1463-1472.
 13. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Europace*. 2006; 8: 746-837.
 14. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H. 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. *Europace*. 2007; 9: 959-998.
 15. Fornwalt BK, Sprague WW, BeDell P, Suever JD, Gerritse B, Merlino JD et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. *Circulation*. 2010; 121: 1985-1991.
 16. Tomassoni, G. How to define cardiac resynchronization therapy response. *JCRM*. 2016; 7: S1-S7.
 17. Hu YR, Hua W, Yang SW, Gu M, Niu HX, Ding LG et al. Predictors of non-response to cardiac resynchronization therapy implantation in patients with class I indications: the markedly dilated left ventricular end-diastolic dimension and the presence of fragmented QRS. *J Geriatr Cardiol*. 2019; 16 (7): 514-521.
 18. Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004; 350 (21): 2140-2150. doi: 10.1056/NEJMoa032423.
 19. Cleland JG, 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; 352 (15): 1539-1549. doi: 10.1056/NEJMoa050496.
 20. Shanks M, Delgado V, Ng AC, Auger D, Mooyaart EA, Bertini M et al. Clinical and echocardiographic predictors of nonresponse to cardiac resynchronization therapy. *Am Heart J*. 2011; 161 (3): 552-557. doi: 10.1016/j.ahj.2010.11.011.

Correspondence:**Marco Antonio Hernández-Mercado****E-mail:** drmarcohdez@gmail.com