BRIEF ARTICLE

Cardiac Resynchronization Therapy. Long-Term Evolution of Responder and Non-Responder Patients

Terapia de resincronización cardíaca. Evolución a largo plazo de los pacientes respondedores y no respondedores

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an effective treatment in patients with heart failure (HF), low left ventricular ejection fraction (LVEF) and wide QRS. However, there are a percentage of these patients who are non-responders, implying worse clinical outcomes.
Objectives: The aim of this study was to assess the differences in echocardiographic parameters of reverse remodeling and event rates [hospitalization for heart failure (HHF), all-cause mortality (ACM), heart transplantation (HTX) and appropriate therapies (AT)] between responder vs. non-responder patients to CRT.
Methods: A total of 343 patients with CRT, classified into responders and non-responders according to clinical and echocardiographic parameters, were included in the study. A 2-year follow-up was performed, in which reverse remodeling and the incidence of HHF, ACM, HTX and AT were evaluated.
Results: Among the 343 patients, 17% were non-responders and 83% responders. At 6 and 12 months there were no significant differences in ventricular diameters, but significant differences in LVEF ($p<0.001$), with greater increase in responders. At 24 months, responders had smaller diastolic diameter ($p=0.004$), smaller systolic diameter ($p=0.003$) and higher LVEF ($p<0.001$). Non-responders had significantly higher incidence of HHF ($p<0.001$), HTX ($p=0.001$) and AT ($p=0.002$), and an excess of ACM at the limit of statistical significance ($p= 0.056$).
Conclusions: Patients responding to CRT presented greater reverse remodeling and better clinical evolution, in accordance with the results of international observational studies.

Keywords: Cardiac Resynchronization Therapy - Heart Failure - Clinical Evolution - Hospitalization

RESUMEN

Introducción: La terapia de resincronización cardíaca (TRC) es un tratamiento eficaz en pacientes con insuficiencia cardíaca (IC), baja fracción de eyección del ventrículo izquierdo (FEVI) y QRS ancho. Sin embargo, hay un porcentaje de estos que son no respondedores, lo que implicaría peores resultados clínicos.
Objetivos: Valorar las diferencias en parámetros ecocardiográficos de remodelado reverso y tasa de eventos [hospitalización por insuficiencia cardíaca (HIC), muerte de todas las causas (MT), trasplante cardíaco (TXC) y terapias apropiadas (TA)] entre pacientes respondedores vs. no respondedores a la TRC.
Material y métodos: Se incluyeron 343 pacientes con TRC. Se los clasificó en respondedores y no respondedores según parámetros clínicos y ecocardiográficos. Se realizó seguimiento a 2 años, en que se evaluó el remodelado reverso y la incidencia de HIC, MT, TXC y TA.
Resultados: De los 343 pacientes, 17% fueron no respondedores y 83% respondedores. A los 6 meses y 12 meses no hubo diferencias significativas en cuando a diámetros ventriculares, pero si en la FEVI ($p<0,001$), que aumentó más en los respondedores. A los 24 meses los respondedores presentaron menor diámetro diastólico ($p=0,004$), menor diámetro sistólico ($p=0,003$) y mayor FEVI ($p<0,001$) Los no respondedores tuvieron significativamente mayor incidencia de HIC ($p< 0,001$), TXC ($p=0,001$) y TA ($p=0,002$)) y un exceso de MT en el límite de la significación estadística ($p= 0,056$).
Conclusiones: Los pacientes respondedores a la TRC presentaron mayor remodelado reverso y mejor evolución clínica, en forma acorde a los resultados de estudios observacionales internacionales.

Palabras clave: Terapia de resincronización cardíaca - Insuficiencia cardíaca - Evolución clínica - Hospitalización

Rev Argent Cardiol 2024;92:211-216. http://dx.doi.org/10.7775/rac.v92.i3.20771

Received: 11/06/2023 – *Accepted:* 02/05/2024

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INTRODUCTION

The prevalence of heart failure (HF) is estimated between 1-3% in the adult population and increases to more than 10% and 30% in those over 70 and 85 years of age, respectively. (1) In recent years, advances in medical treatment have substantially improved the prognosis of these patients. (2,3) However, when optimal medical treatment is insufficient and the patient continues to deteriorate, cardiac resynchronization therapy (CRT) emerges as an effective alternative to improve quality of life, increase left ventricular ejection fraction (LVEF) and reduce mortality in patients who meet the criteria for its indication. (4,5).

The response to CRT depends on multiple factors including adequate patient selection, underlying heart disease, gender, electrode implantation in the appropriate vein of the coronary sinus, A-V and V-V interval programming, and maintenance of a biventricular pacing rate close to 100%, among others. Despite all this, there is a percentage of these patients who do not respond to CRT, which would imply worse long-term clinical outcomes.

OBJECTIVES

The aim of this study was to assess differences in echocardiographic parameters of reverse remodeling and event rates [hospitalization for heart failure (HHF), all-cause mortality (ACM), heart transplantation (HTX) and appropriate therapies (AT, including antitachycardia pacing and appropriate shocks)] between responder vs. non-responder patients to CRT at 2-year follow-up.

METHODS

A retrospective analysis was carried out of prospectively collected data from a single-center cohort of 418 patients with HF in whom CRT devices were implanted between March 2003 and December 2020. Among them, 75 patients were excluded from the analysis due to lack of complete follow-up data. Based on clinical and echocardiographic parameters, patients were classified into responders (those who reduced at least one NYHA functional class, or increased LVEF by 5% in absolute values) and non-responders (those who did not meet these criteria). A 2-year follow-up was performed, in which echocardiographic parameters of reverse remodeling were evaluated: LV diastolic diameter (LVDD), LV systolic diameter (LVSD) and LVEF, and the incidence of significant events: HHF, ACM, HTX and AT.

Statistical analysis

Continuous variables are presented as mean and standard deviation, and were compared with the t test. Categorical variables are expressed as frequencies and percentages, and were compared with the chi-square test or Fisher´s exact test, as appropriate. A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

Among the 343 patients evaluated, 58 (17 %) were non-responders and 285 (83 %) were responders. Baseline population characteristics are shown in Table 1. Mean age at implantation was 64 years, and the percentage of women in the non-responder group was higher. Sixty-eight percent of responders had non-ischemic etiology, while in the non-responder group this occurred in 50%. There were no significant differences between groups in terms of cardiovascular risk factors, nor in the baseline echocardiogram. Most patients were in NYHA functional class I or II. There were differences in the baseline electrocardiogram (ECG): in the non-responder group only 31% had complete left bundle branch block (LBBB), vs. 66% of responders. Baseline QRS duration was shorter in the non-responder group.

At 6 and 12 months there were no significant differences in ventricular diameters, but there were, logically, significant differences in LVEF ($p<0.001$), since an increase in LVEF was one of the criteria for defining response to treatment. At 24 months, there were differences in the group of responders, with significantly lower LVDD ($p=0.004$) and LVSD ($p=0.003$), and higher LVEF ($p<0.001$) (Figure 1).

At the end of the 2-year follow-up, 82% of non-responders had had HHF compared with 13.6% of responders ($p<0.001$). Six non-responder patients (10.3%) died during follow-up (all were cardiovascular deaths, 5 due to HF and 1 to sudden death). Among responders, 12 (4.2%) died, 8 from cardiovascular causes (7 from HF and 1 from electrical storm) and 4 from non-cardiovascular causes. This implies a difference at the limit of statistical significance ($p= 0.056$). Heart transplantation was performed in 10.3% of non-responders vs. 2.1% of responders ($p=0.001$). The incidence of appropriate therapies was 17.2% in non-responders vs. 5.6% in responders ($p=0.002$). (Figure 2).

DISCUSSION

Cardiac resynchronization therapy is an effective treatment for HF refractory to medical therapy, in a subgroup of patients who meet criteria for its indication. This was demonstrated in large randomized studies, including the MIRACLE, COMPANION, CARE HF, REVERSE, MADIT CRT and RAFT trials, on which current clinical practice guideline recommendations are based (6-11). However, not all patients respond to CRT. According to the study analyzed, this percentage varies between 20% and 40%, which depends, in part, on the definition of response to treatment used. Although there is currently no consensus on the definition of CRT response parameters, the most commonly used are clinical parameters (functional class and quality of life), echocardiographic parameters of reverse remodeling, and rates of clinical events, such as HHF and mortality. According to the author, these are used alone or in combination to define response. For years, attempts have been made to detect the factors related to this lack of response: the first ones identified were QRS width,

Table 1. Baseline characteristics

	RESPONDERS (n= 285)	NON-RESPONDERS (n= 58)	p
Age (Years)	63.9 ± 11	64.2 ± 9	0.214
Male gender	194 (68%)	28 (48%)	0.004
Etiology			
Ischemic	90 (31%)	29 (50%)	0.007
Non-ischemic	195 (68%)	29 (50%)	
Risk Factors			
HT	177 (62%)	41 (70%)	0.215
DM	68 (23%)	15 (25%)	0.745
Baseline Medication			
Furosemide	206 (72%)	43 (74%)	0.772
Spironolactone/eplerenone	248 (87%)	47 (81%)	0.231
ACEI/ARB	267 (93%)	53 (91%)	0.522
BB	277 (97%)	57 (98%)	0.638
Prevention			
Primary	256 (89%)	47 (81%)	0.572
Secondary	16 (5.6%)	7 (12%)	0.073
CRT-P	13 (4.5%)	4 (6.8%)	0.455
Baseline FC (NYHA)			
I	11 (3.8%)	7 (12%)	0.010
II	131 (45.9%))	28 (48%)	0.747
III	139 (48.77%)	22 (37%)	0.131
IV	4 (1.4%)	1 (1.7%)	0.852
Baseline ECG			
AF	70 (24%)	21 (36%)	0.067
LBBB	189 (66%)	18 (31%)	< 0.001
QRS duration (ms)	165.3 ±26.3	156.5 ± 31.21	0.003
Echocardiogram			
LVDD (mm)	67.5 ± 9	68.4 ± 10	0.515
LVSD (mm)	54.6 ± 11	57.4 ±12	0.155
LVEF (%)	25.11 ± 6	25.5 ± 6	0.357

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; AF: atrial fibrillation; BB: beta-blockers; CRT-P: cardiac resynchronizing therapy without associated cardioverter-defibrillator; DM: diabetes mellitus; FC: Functional class; HT: hypertension; LBBB: complete left bundle branch block; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter. Qualitative variables are presented as frequency and percentage, n (%); quantitative variables as mean ± standard deviation.

LBBB and functional class, on which the indication criteria are currently based. In 2009 Mullens et al. studied 75 patients with persistent HF symptoms and lack of LV reverse remodeling 6 months after implantation. Most patients had identifiable reasons for suboptimal response: inadequate device configuration (47%), suboptimal medical therapy (32%), arrhythmias causing low percentage of CRT (32%), inadequate LV catheter position (21%), and lack of baseline dyssynchrony (9%). (12) Gender is also a factor to be taken into account; a meta-analysis showed that women had lower total mortality and higher reverse remodeling compared with men. (13) Another fundamental factor is etiology. In 2005 Gasparini et al. showed that patients with non-ischemic cardiomyopathy had greater increase in LVEF and improvement in functional class. (14) This was confirmed by subsequent studies. (15) There are now indications that some genetic variables might also be related, although much remains to be studied. (16)

In our study, to our knowledge the largest and longest follow-up study in Argentina, we used combined parameters of functional class improvement and reverse remodeling to define response. The percentage of non-responders was 17%, and the long-term evolution of these patients was worse, with a significantly higher rate of HHF, HTX, ACM and AT compared with responders. Although our work had a low rate of non-responders compared with the literature, the adverse clinical outcomes in this population encourages us to continue working in order to identify factors related with suboptimal response to CRT, to perform early interventions and try to improve their long-term prognosis.

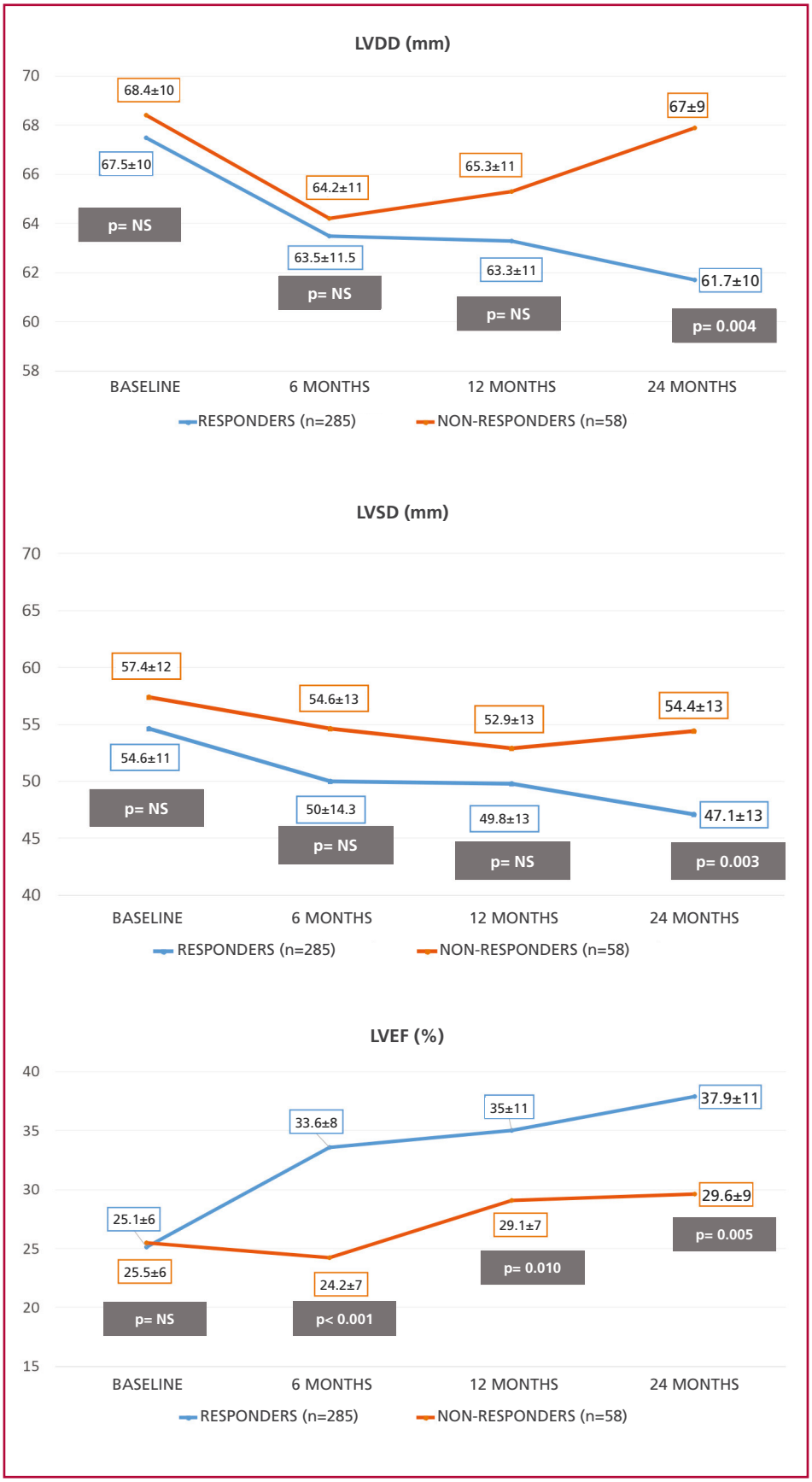

Fig. 1. Echocardiographic evolution in responders and non-responders.

LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter

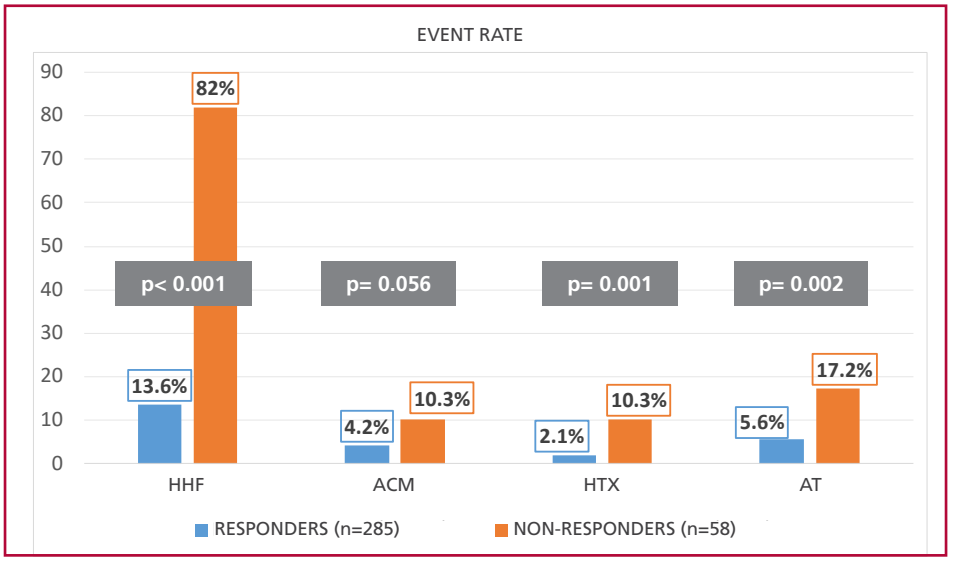

Fig. 2. Incidence of events in responders and non-responders.

ACM: all cause mortality; AT: appropriate therapies; HHF: hospitalization for heart failure; HTX: heart transplantation

CONCLUSION

In our population, responder patients had significantly better echocardiographic parameters of reverse remodeling. This may explain the significantly lower rate of HHF, ACM, HTX, and AT compared with non-responders.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

Financing

None.

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