ORIGINAL ARTICLE

Cardiac Resynchronization Therapy. Incidence and Mechanisms Involved in the Reduction of Functional Mitral Regurgitation

Terapia de resincronización cardiaca. Incidencia y mecanismos involucrados en la reducción de la insuficiencia mitral funcional

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ABSTRACT

Background: Functional mitral regurgitation (FMR) is common in heart failure, and moderate/severe (M/S) FMR is associated with worse prognosis.
Objective: The aim of this study was to describe the prevalence of FMR and the mechanisms involved in its reduction in responders to cardiac resynchronization therapy (CRT) at 6 months compared with 12 and 24 months.
Methods: Between 2009 and 2018, 338 patients received CRT. Patients who showed NYHA functional class (FC) reduction ≥1 or left ventricular ejection fraction (LVEF) absolute increase ≥5% were considered responders. Functional mitral regurgitation was graded using a 4-point scale into none-, mild-, M- and S-FMR, and was related to echocardiographic measurements. Baseline patient characteristics were: age 64±10 years, men 71%, NYHA FC II-III 92%, left bundle branch block (LBBB) 67%, QRS ≥150 ms 75%, LV diastolic diameter (LVDD) 68±9 mm, LV systolic diameter (LVSD) 52±12 mm, and LVEF 24±7%.
Results: The prevalence of FMR was 92.6%. At 6 months, 86% were responders, 23% improved from M/S-FMR to mild/none-FMR and there was strong reverse remodeling: LVDD 68±10 vs. 63±11 mm, (p=0.0001), LVSD 55±12 vs. 50±13 mm, (p=0.0006) and LVEF 25±11 vs. 33±10%, (p=0.00001). Comparing 6 with 12 months, 89.4% were responders and 8% improved M/S-FMR to mild/none-FMR. Comparing 6 with 24 months, 88% were responders and 14.6% improved M/S-FMR to mild/none-FMR. Between 6 and 12 and 6 and 24 months, there was no significant reverse remodeling.
Conclusions: The prevalence of FMR was high. The highest reverse remodeling and FMR reduction was observed at 6 months, the former being the main mechanism of FMR reduction. This improvement persisted at 12 and 24 months.

Key words: Cardiac resynchronization therapy - Functional mitral regurgitation - Reverse remodeling - Responders to cardiac resynchronization therapy - Heart failure

RESUMEN

Introducción: La Insuficiencia Mitral Funcional (IMF) es común en pacientes con insuficiencia cardíaca (IC). La IMF moderada/grave (M/G) se asocia a peor pronóstico.
Objetivo: Describir la prevalencia de IMF y los mecanismos involucrados en su reducción en respondedores a la terapia de resincronización cardíaca (TRC) a los 6 meses comparados con 12 y 24 meses.
Métodos: Entre 2009 y 2018 fueron tratados 338 pts. Respondedores: reducción de CF NYHA ≥1 grado o aumento de la fracción de eyección ventricular izquierda (FEVI) ≥5% (absoluto). La IMF se graduó en 4 puntos: No-IMF, leve, M y G y se la relacionó con las mediciones ecocardiográficas. Características Basales: edad 64±10 años, hombres 71%, CF-NYHA II-III 92%, bloqueo de rama izquierda (BRI) 67%, QRS ≥150 ms 75%, diámetro diastólico del VI (DDVI) 68±9 mm, diámetro sistólico del VI (DSVI) 52±12 mm, FEVI 24±7%.
Resultados: La prevalencia de IMF fue del 92,6%. A los 6 meses, 86% fueron respondedores y 23% de ellos mejoraron de IMF-M/G a IMF-Leve/No-IMF. Hubo un fuerte remodelado inverso: DDVI 68±10 vs 63±11, (p=0,0001), DSVI 55±12 vs 50±13, (p=0,0006) y FEVI 25±11 vs 33±10%, (p=0,00001). Comparando 6 con 12 meses 89,4% fueron respondedores, 8% mejoraron de IMF-M/G a IMF-Leve/No-IMF. Comparando 6 con 24 meses 88% fueron respondedores, 14,6% mejoraron de IMF-M/G a IMF-Leve/No-IMF. Entre 6 y 12 y 6 y 24 meses no hubo remodelado inverso significativo.
Conclusiones: La prevalencia de IMF fue elevada. El mayor remodelado inverso y reducción de la IMF se observaron a los 6 meses, siendo el primero el principal mecanismo en la reducción de la IMF. Esta mejoría se sostuvo a los 12 y 24 meses.

Palabras clave: Terapia de resincronización cardíaca - Insuficiencia mitral funcional - Remodelado inverso - Respondedores a la terapia de resincronización cardíaca - Insuficiencia cardíaca

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INTRODUCTION

Functional mitral regurgitation (FMR) is common in patients with heart failure (HF), both due to ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM). (1) Moderate (M) or severe (S) FMR is associated with worse prognosis due to a significant increase in morbidity and mortality. (2)

The prevalence of FMR is estimated between 20-50% in patients with ICM and between 55-65% in patients with NICM, and is associated with a threefold increased risk of HF in both groups and 1.6 and two-fold increased risk of death in ICM and NICM, respectively, at a 5-year follow-up. (3,4)

However, to date there is no effective FMR medical or surgical treatment to reduce these risks.

The mitral valve is a very complex structure whose function depends on the interaction between the leaflets, the mitral annulus, the subvalvular apparatus (chordae tendineae and papillary muscles), and the left ventricle. The leaflets close with a significant overlap, called coaptation reserve. The reduction of this reserve is due to the imbalance between tethering forces and closing forces on the leaflets, in favor of the former (Figure 1).

Several studies have shown that cardiac resynchronization therapy (CRT) implantation can decrease this imbalance by reducing left ventricular (LV) dyssynchrony through the following mechanisms: increase of closing forces (global synchrony), reduction of tethering forces, and remodeling of annulus geometry (local synchrony), in addition to diastolic mitral regurgitation correction by atrioventricular synchrony. (5-7)

Two phases have been proposed in the reduction of FMR after CRT implantation. a) immediate FMR reduction would occur within the first 6 months and would be due to the fast resynchronization effect on papillary muscle contraction, with decreased tethering vectors and reduced volume overload; and b) longer-term reduction would depend on reverse LV remodeling, with decreased dilation and sphericity, minimization of tethering forces on the mitral valve apparatus, and improved closing forces due to increased contractility. (8)

The purpose of our study was to describe the prevalence of FMR in patients with CRT implantation and the mechanisms involved in its reduction in responders at 6 months, compared with long-term responders (12 and 24 months).

METHODS

A retrospective single-center study including 338 HF patients implanted with CRT was performed between 2009 and 2018. Clinical, electrocardiographic and echocardiographic parameters were evaluated: NYHA FC, LV diastolic diameter (LVDD), LV systolic diameter (LVSD), and LV ejection fraction (LVEF). Functional mitral regurgitation was assessed according to guidelines measuring effective regurgitant orifice area, regurgitant volume, and regurgitant fraction. A 4-point scale was used to grade its severity into none-, mild-, M-, and S-FMR. These parameters were evaluated prior to implantation and at 6 months, and the latter was compared with those obtained at 12 and 24 months.

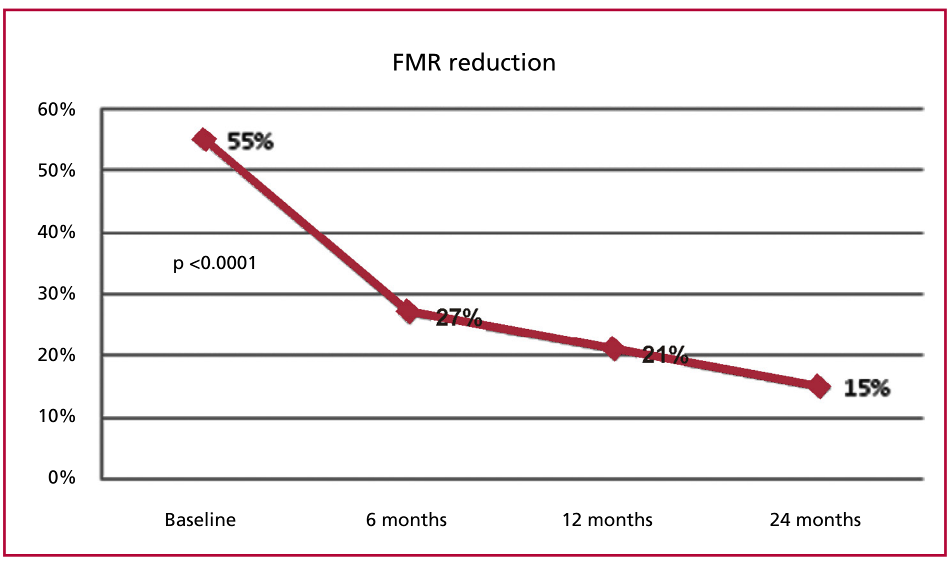
Patients who at least reduced NHYA FC ≥1 or increased absolute LVEF ≥5% were considered responders, those who increased absolute LVEF ≥10% were considered super-responders, and those with LVEF ≥50% were considered normalizers. All patients were under optimized medical treatment.

Patients who did not present complete clinical and echocardiographic assessment in each control were excluded, leaving only patients with a complete control evaluation: 237 at 6 months, 170 at 12 and 132 at 24 months.

Changes in FMR and its mechanisms were evaluated in responder patients.

Statistical analysis

Continuous variables were presented as mean and standard deviation or median and interquartile range, and categorical variables as numbers and percentages. Student's t test and



FMR: Functional mitral regurgitation

Fig. 1. Functional mitral regurgitation reduction over time

the Mann-Whitney test were used to compare continuous variables with normal distribution and with non-normal distribution, respectively. Categorical variables were compared with the chi-square test or Fisher's test, as appropriate. Statistical significance was established at $p < 0.05$.

RESULTS

Baseline characteristics are shown in Table 1.

At 6 months post-implantation, the changes in FMR and the mechanisms involved in its reduction were evaluated in 237 out of the 338 implanted patients. In this period, 204 out of 237 patients were responders (86%), 86 (36%) were super-responders, and 22 (9%) normalized their LVEF. Among the 204 responders, 83 (40.6%) reduced their FMR ≥1 grade and 46 (23%) moved from M/S-FMR to mild/none-FMR. In addition, a strong reverse remodeling was observed.

When comparing 6 vs. 12 months, 152 of 170 patients (89.4%) were responders. Among these, 35 (23%) reduced their FMR ≥1 grade and 12 (8%) moved from M/S-FMR to mild/none-FMR. Contrary to what was observed at 6 months, no significant reverse remodeling was observed in this period.

Finally, analyzing 6 vs. 24 months, 116 of 132 patients (88%) were still responders, 26 (22%) improved their FMR ≥1 grade and 17 (14.6%) changed from M/S-FMR to mild/none-FMR. Small changes in LV diameters and a trend towards better LVEF were observed between 6 and 24 months, without statistically significant differences.

The comparison of the results obtained in the different periods analyzed regarding M/S-FMR and volumetric data is shown in Table 2. In each time period analyzed, there were few patients who worsened their FMR, from mild/none-FMR to M/S-FMR: 2% between baseline and 6 months, 5% between 6 and 12 months and 6% between 6 and 24 months .

Figure 1 shows the evolution of M/S-FMR from baseline to 24 months and Figure 2 shows the evolution of LVEF over time.

Table 1. Baseline characteristics (n=338)

Clinical characteristics	n	%/SD
Male	239	71%
Age (years)	64	10
ICM	215	63.6%
NICM	123	36.4%
Primary prevention	301	89%
NYHA FC II/III	311	92%
ECG		
SR	256	76%
CLBBB	227	67%
QRSd msec (mean, SD)	156	27
QRS ≥150 ms	253	75%
Echocardiographic characteristics		
LVDD mm (mean, SD)	68	9
LVSD mm (mean, SD)	52	12
LVEF % (mean, SD)	24.7	9
Total MR	313	92.6%
Mild MR	140	44.8%
M MR	110	35.1%
S MR	63	20.1%

ICM: Ischemic cardiomyopathy. NICM: Non-ischemic cardiomyopathy
SR: Sinus rhythm
CLBBB: Complete left bundle branch block
LVDD: Left ventricular diastolic diameter
LVSD: Left ventricular systolic diameter
LVEF: Left ventricular ejection fraction
MR: Mitral regurgitation, M: Moderate, S: severe
SD: standard deviation

DISCUSSION

Functional mitral regurgitation is common in patients with HF, both of ischemic and non-ischemic etiology, and CRT appears as the best therapy to reduce it.

There are several studies that demonstrate the benefit of CRT for this purpose. In the CARE HF (Cardiac Resynchronization-Heart Failure) study, CRT reduced interventricular mechanical delay, end-systolic volume, and mitral regurgitation area, with the consequent increase in LVEF and improvement in symptoms and quality of life compared with medical treatment, a result that has been corroborated by other publications (9-14).

It is important to emphasize that FMR severity at three months was the strongest independent predictor of mortality. This highlights the prognostic value of FMR response in these patients and the importance of proper timing for their intervention. (15)

However, it is important to note that such studies have many limitations. They include different patient populations, mostly in NYHA FC III-IV and QRS ≥120 ms, which differs from the indications of current clinical practice guidelines. (16) In addition, many of them show an overlap in FMR grading, comparing mild/M-FMR with M/S-FMR. Finally, the method of FMR echocardiographic quantification is not always the same. (8).

For this reason, in our study we included patients predominantly in NYHA FC II/III (92%), with a high percentage of patients with QRS ≥150 ms (75%), and FMR assessment performed by quantitative methods and graded in the previously described 4-point scale.

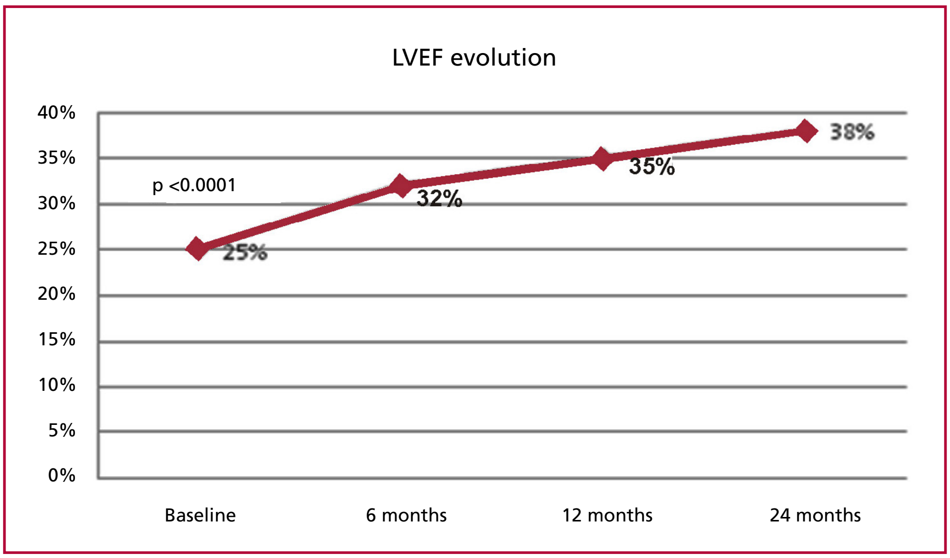
Our population showed a high prevalence of FMR (92.6%), with a high percentage of responders at 6 months (86%), which was sustained over time. The greatest incidence of FMR reduction, as well as the highest degree of reverse remodeling was observed at 6 months. Although at 12 and 24 months this improvement was preserved, it did not show a significant change.

Therefore, although the synchronous contraction of the papillary muscles and the reduction of the traction vectors could have had an immediate influence, as suggested in previous studies, LV reverse remodeling was early and constituted the main mechanism for FMR reduction, from the first months.

Table 2. Summary of results

Total CRT-P/D FMR 313/338pts (92.8%)	FMR-S	FMR-M	LVDD (mm)	LVSD (mm)	LVEF (%)
Baseline vs. 6 m			BASELINE		
Responders 204/237 (86%)	36/204 (18%)	62/ 204 (30%)	70±10	58±12	24±11
			6 MONTHS		
	16/204 (8%)	40/204 (20%)	63.5±11	50±13	32±11
	(p=0.002)	(p=0.01)	(p=0.0001)	(p=0.001)	(p=0.00001)
6 vs. 12 m			6 MONTHS		
Responders 152/170 (89%)	11/152 (7%)	26/152 (17%)	63±12	50±14	34±10
			12 MONTHS		
	10/152 (6.5%)	22/152 (14%)	63±12	49±14	36±11
	(p= 0.8)	(p=0.5)	(p=0.5)	(p=0.9)	(p=0.2)
6 vs. 24 m			6 MONTHS		
Responders116/132 (88%)	8/116 (7%)	20/116 (17 %)	63±12	49±14	35±10
			24 MONTHS		
	5/116 (4%)	13/116 (11%)	61±11	46±143	38±12
	(p= 0.39)	(p= 0.18)	(p= 0.1)	(p= 0.2)	(p= 0.06)

Comparison of S- and M-FMR, LVDD, LVSD and LVEF in the different time periods.
CRT: Cardiac resynchronization therapy
P/D: Pacemaker/defibrillator
FMR: Functional mitral regurgitation
M: Moderate, S: Severe
LVDD: Left ventricular diastolic diameter
LVSD: Left ventricular systolic diameter
LVEF: Left ventricular ejection fraction



LVEF: Left ventricular ejection fraction

Fig. 2. Left ventricular ejection fraction evolution over time

Conflicts of interest

None declared.

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

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