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Determinants and Clinical Outcomes of Functional Mitral Regurgitation Improvement Following Cardiac Resynchronization Therapy

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ABSTRACT

Background: Functional Mitral Regurgitation (FMR) is associated with poor prognosis in patients with Heart Failure (HF) and reduced Left Ventricular Ejection Fraction (LVEF). Cardiac Resynchronization Therapy (CRT) has been shown to lead to long-term and accurate improvement in FMR.

Objective: This study aims to identify the determinants of FMR improvement after CRT and determine their impacts on clinical outcomes.

Methods: In this retrospective single-centered study of consecutive CRT implantations, echocardiographic evaluation was performed before CRT implantation and at 6-12-month follow-up. FMR improvement was defined as ≥ 1 grade reduction in MR class. Independent predictors of FMR improvement were determined by multivariate analysis. The composite outcome of HF hospitalization and mortality was used to determine the prognosis.

Results: This study was conducted on 192 patients with a median follow-up of 50 ± 35 months. At baseline, FMR was present in 85% of the participants (48% mild, 30% moderate, and 7% severe). Improvement after CRT was observed in 74% of the patients with significant FMR. The variables associated with CRT improvement were atrial fibrillation, diabetes, and wider QRS, septal right ventricular lead, and posterolateral left ventricular lead. After multivariate analysis, only QRS duration was an independent predictor of FMR improvement (OR: 1.08, 95% CI: 1.00 - 1.17, P = 0.041). 'Improvers' had a higher survival-rate free of composite outcome at follow-up (74% vs. 33%, P = 0.015). Yet, the clinical benefit of FMR improvement was independent from CRT responsiveness (p-interaction = 0.338).

Conclusion: FMR was prevalent in patients undergoing CRT implantation, and three-fourths of the patients experienced a reduction in regurgitation severity. The only independent predictor of FMR improvement was QRS duration. Moreover, improvement was associated with better prognosis, independently from CRT responsiveness.

1. Background

Functional Mitral Regurgitation (FMR) is common in patients with advanced Heart Failure (HF) with reduced Left Ventricular Ejection Fraction (LVEF), regardless of etiology (1). The presence of FMR is a strong predictor of prognosis in these patients. Additionally, a linear correlation has been found between the degree of FMR and mortality and morbidity (2-4). FMR may be caused by multiple mechanisms, such as Left Ventricular (LV) systolic dysfunction, changes in LV shape and size, mitral annulus dilation, mechanical desynchrony, and, less frequently, isolated left atrium enlargement due to Atrial Fibrillation (AF) (5-7). These pathological changes contribute to the increase of tethering forces from papillary muscle displacement that cannot be efficiently counteracted by the closing mechanism of the valve leaflets, leading to significant central regurgitation.

Cardiac Resynchronization Therapy (CRT) is a well-established treatment for HF patients with reduced LVEF and large QRS, improving their prognosis and quality of life (8-10). CRT has also been shown to lead to accurate and long-term improvement in FMR (11, 12). CRT-induced synchronization increases the closing forces and promotes a

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better coordinated activation of the components of the mitral valve structure (5, 13-16). At long-term, reverse remodeling of the left ventricle will minimize the tethering forces of the mitral valve apparatus. Both mechanisms participate in the ultimate reduction of FMR (13, 17). However, most studies have indicated that FMR improved in only up to 50% of patients after CRT (12, 13, 18) and the determinants of this response have remained to be established. To further underline the importance of this issue, no reduction of FMR after CRT has been associated with a worse long-time prognosis (19). On the other hand, significant FMR (moderate to severe) at baseline has been reported to be on itself a predictor of CRT response and FMR improvement (20).

2. Objectives

This study aims to discover the determinants of significant FMR improvement after CRT and to evaluate their impacts on clinical outcomes.

3. Patients and Methods

3.1. Study Population and Study Design

This retrospective observational study was conducted on 316 consecutive patients who underwent CRT with or without a defibrillator (CRT-D or CRT-P) at Centro Hospitalar Universitário do Porto between January 2002 and March 2016. All patients had HF with reduced LVEF (< 35%) and QRS ≥ 130 ms and remained in the New York Heart Association (NYHA) class II-IV despite medical therapy. Since the study objective was to evaluate FMR, patients with significant structural disease of mitral valve, mitral prosthetic valves, or valve repair were excluded. The patients with significant FMR (moderate/severe) were selected for their improvement to be evaluated.

Demographic and clinical data were extracted from the medical records. Echocardiographic evaluation was made at baseline and 6 - 12 months after CRT. Patients with missing data at follow-up or no echocardiographic re-evaluation were excluded. All echocardiographic studies were performed in an echocardiography laboratory certified by the European Association of Cardiovascular Imaging (EACVI) and were analyzed by experienced cardiologists.

MR was classified into mild, moderate, and severe categories using the EACVI recommendations (21). FMR improvement was defined as a reduction of at least one grade in MR class. LVEF was estimated by Simpson's Biplane method in all patients. Patients with very poor echocardiographic window were excluded, unless a clear improvement of LVEF was evident by other methods. CRT response was defined as an absolute increase in LVEF ≥ 5% and an improvement in NYHA class ≥ 1. Furthermore, the composite outcome of HF hospitalization and mortality was used to determine the prognosis.

3.2. Device Implantation

Transvenous approach via the left cephalic or subclavian veins was used to implant the leads of CRT devices (with or without defibrillator according to ongoing guidelines and patient characteristics). A right atrial lead was positioned in the right atrial appendage (only omitted in patients with permanent AF). The Right Ventricular (RV) lead was located in the RV apex or medium Interventricular (IV) septum, according to the operator's choice. Unipolar, bipolar, or quadripolar LV leads were implanted preferably in the posterolateral or lateral veins.

3.3. Echocardiography Analysis

Standard 2D and Doppler transthoracic echocardiograms were performed at an EACVI certified echocardiography laboratory. All patients had an echocardiographic evaluation at baseline and 6-12-month follow-up. LVEF was quantified using de Simpson's biplane method. Following EACVI recommendations, FMR was graded according to qualitative, semi-quantitative, and quantitative methods as no, mild, moderate, and severe MR. LV end-systolic diameter and LV end-diastolic diameter were also obtained at baseline and follow-up.

3.4. Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp). Independent Student's t-test and Mann-Whitney U test were used to compare normally and non-normally distributed continuous variables, respectively. Additionally, categorical variables were compared by chi-square or Fisher's exact tests. Moreover, independent predictors of significant FMR improvement were determined by logistic regression analysis. Variables with $P < 0.1$ in the univariate analysis were included in the multivariate model. The Kaplan-Meier method was used to estimate the survival curves. All tests were two-sided and $P < 0.05$ was considered to be statistically significant.

4. Results

Out of the 316 consecutive patients undergoing CRT during the study period, 192 fulfilled the inclusion criteria of the research. The mean follow-up time was 50 ± 35 months. The mean age of the patients was 68 ± 10 years. Besides, 60% of the patients were male, 62% had non-ischemic cardiomyopathy, and 81% were in NYHA class III.

At baseline, FMR was present in 85% of the patients (48%, 30%, and 7% had mild, moderate, and severe MR, respectively). An improvement in FMR after CRT was observed in 74% of the patients with significant FMR (moderate/severe, n = 72). The demographic and procedural characteristics of the patients with and without FMR improvement have been summarized in Table 1. The group of patients who did not experience improvement in FMR had a higher rate of AF (84% versus 48%, P = 0.037) and diabetes (53% versus 24%, P = 0.031). On the other hand, the patients with improved FMR had a wider QRS at baseline (167.5 ± 16.4 versus 146.6 ± 17 ms, P = 0.003). There was also a trend towards a higher percentage of RV lead pacing in the medium IV septum and LV lead in the posterolateral position in this group of patients. In multivariate analysis including AF, baseline LV end-systolic diameter, QRS duration, LV lead in the posterolateral position, and RV lead pacing in the IV septum, only QRS duration was an independent predictor of FMR improvement (Table 2).

Considering CRT response, the group of patients with FMR improvement showed a greater increase in LVEF

Table 1. Demographic, Clinical, Medication, and Procedural Data

	No FMR Improvement (n = 19)	FMR Improvement (n = 53)	P-value
Male gender	57.9%	50.9%	0.320
Mean age	68.2 ± 8.9	70.5 ± 9.2	0.360
Non-ischemic etiology	52.6%	62.3%	0.320
Diabetes	52.9%	23.9%	0.031
Hypertension	88.2%	71.7%	0.151
Dyslipidemia	64.7%	63%	0.573
Smoke exposure	29.4%	15.2%	0.179
Chronic kidney disease	35.3%	34%	0.575
Atrial fibrillation	84.2%	58.2%	0.037
NYHA class III/IV	89.5%	86.8%	0.560
B-blockers	87%	83.2%	0.670
ACEI/ARA	87.2%	90.3%	0.676
Aldosterone antagonist	59%	56%	0.563
LVEF (%)	25.8 ± 3.2	26.4 ± 6.7	0.639
LV end-systolic diameter (mm)	55.3 ± 6.1	51.5 ± 8.9	0.198
LV end-diastolic diameter (mm)	63.9 ± 5.4	63.2 ± 9.5	0.760
Left bundle branch block	76.4%	83.7%	0.370
QRS duration (ms)	146.6 ± 17	167.5 ± 16.4	0.003
Upgrade from right ventricular pacing	31.2 %	22%	0.340
Right ventricular lead pacing in IV septum	44.7%	71.4%	0.081
LV lead in a posterolateral position	34.2%	61.5%	0.083

Abbreviations: ACEI/ARA, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; IV, interventricular; LV, left ventricular; NYHA, New York Heart Association.

Table 2. Multivariate Analysis of the Significant Univariate Predictors of Mitral Regurgitation

	Multivariate Analysis		
	OR	**95% CI**	**P-value**
Atrial fibrillation	0.185	0.012 to 2.89	0.425
Baseline LV end-systolic diameter	0.91	0.71 to 1.16	0.229
QRS duration (ms)	1.08	1.00 to 1.17	0.041
LV lead in a posterolateral position	2.018	0.13 to 30.31	0.539
Right ventricular lead pacing in the IV septum	3.874	0.51 to 29.30	0.612

Abbreviations: IV, interventricular; LV, left ventricular.

Table 3. Variations in LVEF and LV Diameters according to MR Improvement After CRT

After CRT	No MR Improvement	MR Improvement	P-value
CRT responders	38.9%	56.9%	0.150
Δ LVEF (%)	4.7 ± 4.8	8.3 ± 8.5	0.032
Δ LV end-systolic diameter (mm)	1.4 ± 7.0	9.5 ± 15.6	0.017
Δ LV end-diastolic diameter (mm)	0.4 ± 3.4	4.7 ± 8.6	0.04

Abbreviations: CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LV, left ventricular.

and reduction of both LV end-systolic and end-diastolic diameters (Table 3). There was also a tendency towards a higher rate of responders (defined as an absolute increase in LVEF ≥ 5% and an improvement in NYHA class ≥ 1) although the difference was not statistically significant.

The composite outcome of HF hospitalization and global mortality during the five-year follow-up occurred in 26% of the patients with FMR improvement and 67% of those without improvement (P = 0.015). The Kaplan-Meier survival curves free of the composite outcome for both groups have been depicted in Figure 1. Accordingly, the clinical benefit of FMR improvement was independent from CRT responsiveness (P = 0.338).

5. Discussion

This study represented a real-world HF population submitted to CRT. A significant percentage of these patients (37%) had significant (moderate to severe) FMR at baseline. Among these patients, 74% experienced an improvement in FMR after CRT. Since FMR is associated with HF symptoms and worse prognosis, these findings corroborate the important role that resynchronization therapy plays in its treatment. As recommended by the European Association of Cardiology (ESC) guidelines, it should be the first option considered in these patients before surgery or percutaneous treatment of the mitral valve. Similar results have also been reported in the previous studies (12, 20, 22). The higher percentage of CRT improvement in the present sample (74% versus ~50% described in other series) might be related to the fact that only patients with significant FMR were selected at baseline, which has been reported to be on itself predictive of MR improvement after CRT (20).

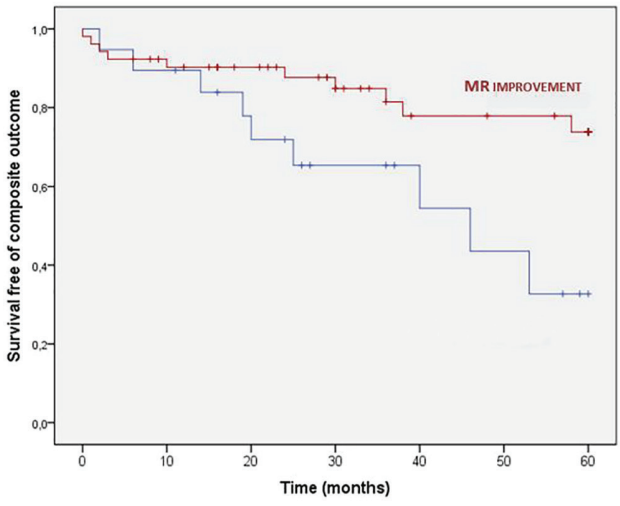

Figure 1. Kaplan-Meier Survival Curves of the Composite Outcome (All-Cause Death and Heart Failure) for Patients with and without Mitral Regurgitation Improvement MR, Mitral Regurgitation

When looking at the differences between the study groups, it was interesting to see that AF was more prevalent amongst the non-improvers. Previous studies have also reported that FMR improvement was more likely to be achieved in patients in the sinus rhythm (23). This might be explained by the fact that FMR in patients with AF is related to atrial dilation and remodeling, which will not be influenced by resynchronization therapy (7, 23). Most importantly, it is known that a high percentage of biventricular pacing is harder to achieve in AF patients, which might reduce both CRT response rate and FMR improvement.

The current study findings revealed no significant difference between the study groups regarding baseline LVEF and degree of LV dilation. Among the FMR improvers, there was a significantly longer QRS duration and a trend towards a higher percentage of LV lead in the posterolateral position and RV lead in the IV septum. However, in multivariate analysis, only QRS duration remained as an independent predictor of FMR improvement. It has been shown that FMR severity was correlated to QRS duration in patients with dilated LV and left bundle branch block or right ventricular pacing (6). The fact that a longer QRS predicts FMR improvement after CRT shows that the restoration of ventricular synchrony plays a major role in the immediate reduction of MR severity, which has been demonstrated in the previous studies to be independent from LV reverse remodeling (24) and to be a determinant of CRT response (16).

At clinical and echocardiographic follow-up after CRT (6 - 12 months), FMR improvers showed a more favorable reverse LV remodeling, with significantly improved LVEF and reduction of LV end-systolic and end-diastolic diameters. The reduction of LV dilation and sphericity promoted by CRT minimized the tethering forces of the mitral valve apparatus, leading to a long-term improvement of FMR (5, 13, 15). CRT response (defined as both clinical and echocardiographic improvement) also occurred more frequently in patients with FMR improvement although the difference was not statistically significant (57% versus 39%, P = 0.150). This could be explained by the relatively small size of the study.

Regarding the clinical outcomes, the composite of HF hospitalizations and mortality during the five-year follow-up occurred more frequently among the non-improvers, as depicted by the clearly diverging Kaplan-Meier curves (Figure 1). Moreover, the clinical benefit of FMR improvement was independent from CRT responsiveness (P = 0.338), which was in line with the results of other studies (20, 25) demonstrating that the persistence of significant FMR after CRT was strongly predictive of worse long-term survival. Irrespective of CRT response, persistence of moderate to severe FMR after resynchronization seems to be an important indicator of bad prognosis. In these patients, an early alternative FMR treatment should be considered in order to improve their clinical response and outcomes.

In conclusion, significant FMR was prevalent among the patients with advanced HF undergoing CRT implantation. Additionally, there was a reduction in valvular regurgitation severity in three-fourths of the patients. Moreover, QRS duration was the only independent predictor of MR improvement. FMR improvement was also associated with reverse LV remodeling and a better prognosis, independently from CRT responsiveness.

5.1. Limitations

This study had some limitations. Firstly, it was a retrospective observational study, which might have led to a potential bias in patient selection. Nonetheless, it reflected the real-world clinical practice of the patients with advanced HF in a tertiary care center. Secondly, mitral insufficiency grade was subjectively assessed through quantitative and semi-quantitative methods without core lab analysis. However, very experienced echocardiographists at an EACVI-certified echocardiography laboratory did all the echocardiographic evaluations. To reduce the inter-observer variability, MR grade was divided into mild, moderate, and severe categories and MR improvement was only analyzed in patients with at least moderate FMR at baseline. Thirdly, the researchers did not account for device programming or pharmacological therapy changes after CRT implantation, which were made as needed by the cardiologists conducting the CRT consult. Finally, the small sample size of the study inevitably lowered the statistical power of the analysis.

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Authors' Contribution

MT: Study concept and design; Acquisition of data; Analysis and interpretation of data; Drafting of the manuscript; Critical revision of the manuscript for important intellectual content; Statistical analysis; RS: Study concept and design; Acquisition of data; Analysis and interpretation of data; Drafting of the manuscript; Statistical analysis; IS: Study concept and design; Acquisition of data; Analysis and interpretation of data; Statistical analysis; MJS: Acquisition of data; Critical revision of the manuscript for important intellectual content; MFO: Acquisition of data; Analysis and interpretation of data; Statistical analysis; RC: Acquisition

of data; Analysis and interpretation of data; Statistical analysis; CR: Acquisition of data; Critical revision of the manuscript for important intellectual content; HR: Critical revision of the manuscript for important intellectual content; Study supervision VD: Critical revision of the manuscript for important intellectual content; ST: Study supervision.

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