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Original Article

MitraClip implantation in real-world: clinical relevance of different patterns of left ventricular remodeling

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ABSTRACT

Objective: The role of left ventricular (LV) volumes and ejection fraction (EF) in the selection of patients for the MitraClip procedure remains matter of debate. The goal of this study is to assess the pattern of LV remodeling and its clinical implications after MitraClip procedures, and to evaluate the role of LV ejection fraction (EF) in patient selection.

Methods: Complete echocardiography was performed before, at discharge, 1,6, and 12-months in 45 patients treated with MitraClip for severe mitral regurgitation (MR) [age 78.2 ± 8.3 yrs, NYHA 3.74 ± 0.44, EF 36.5 ± 12.8%]. From baseline to 6-month, reverse and adverse LV-R were defined as a ≥15% decrease in LV end-systolic volume and a ≥10% increase in LV end-systolic volume, respectively.

Results: At 6-month, sustained reduction of MR ≤ 2 was observed in all patients, but two; reverse, adverse, and no LV-R occurred in 51% (N = 23), 18% (N = 8), and 31% (N = 14) of patients, respectively. Baseline LV end-diastolic volume was an independent predictor of reverse LV-R [P = 0.004], whereas EF was not. During follow-up (17.5 ± 9.3 months) period, 50% of adverse/no LV-R patients were free of the composite endpoint (mortality and hospitalization for heart failure) compared to 95.7% of reverse LV-R patients (P = 0.006). In Cox analysis, adverse LV-R and adverse/no LV-R were associated with composite endpoint with adjusted hazard ratios of 5.6 (95% CI 1.65-19.00) and 10.08 (95% CI 1.29–78.6), respectively.

Conclusion: After MitraClip implantation, sustained adverse or no LV-R occurred in one-in-two patients and was associated with poor prognosis. Large LV volumes may help us to avoid the futility of the procedure.

1. Introduction

Reverse left ventricular (LV) remodeling (LV-R) is a well-known phenomenon that occurs in a wide spectrum of heart diseases and is generally associated with a better prognosis. Reverse LV remodeling has been reported in non-valvular cardiomyopathies treated with cardiac resynchronization therapy (CRT).[1] Reverse remodeling post-CRT was found to be mainly related to the initial extent of the LV conduction delay, as well as LV scar volume and location, and has been linked to a lower risk of heart failure (HF).[2] Moreover, reverse LV remodeling represents a true goal in STEMI patients treated with primary angioplasty in order to improve the prognosis, especially in patients with a large area of myocardium at risk.[3] Not surprisingly, in the setting of percutaneous treatment for valve disease, reverse LV remodeling may play a relevant role for prognosis. Indeed, reverse LV remodeling has been well described after transcatheter aortic valve implantation (TAVI) procedures, and its occurrence is associated with a good prognosis.[4] The surgical or percutaneous repair of severe mitral regurgitation (MR) has been shown to prevent and even reverse adverse LV remodeling, improve cardiac function and functional status, and reduce the risk of heart failure and hospitalization.[5-7] However, even after publication of two randomized trials assessing outcome after MitraClip implantation, data on prognosis remains conflicting.[8,9] The aim of this prospective single-center registry is to assess the pattern of LV remodeling after MitraClip procedure and its clinical implications. Furthermore, the role of LV ejection fraction (EF) in the selection of patients for MitraClip implantation was assessed.

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Abbreviations and Acronyms

LV-R	left ventricular remodeling
CRT	cardiac resynchronization therapy
HF	heart failure
TAVI	transcatheter aortic valve implantation
MR	mitral regurgitation
EF	ejection fraction
CAD	coronary artery disease
PAPs	Systolic pulmonary arterial pressure
ESV	end systolic volume
GLS	global longitudinal strain
EDV	end diastolic volume
ICC	intraclass correlation coefficient
EROA	effective regurgitant orifice area

2. Methods

2.1. Study population

In our study, we included all consecutive patients who underwent percutaneous mitral valve repair with MitraClip linked to severe symptomatic mitral valve regurgitation at our center, Careggi Hospital, a large tertiary care referral center. All patients underwent serial baseline, after procedure, 1, 6, and 12-month complete 2D-echo evaluations. The MitraClip procedure was indicated if a patient's logistic EuroSCORE or STS PROMsurgical risk was too high, based on both a clinical and heart-team evaluation. In the case of severe coronary artery disease (CAD), percutaneous coronary intervention was performed at least three months before the mitral valve procedure. Clinical characteristics of the patients were collected prospectively in our registry. A total of two patients were excluded because of an early switch to surgical mitral valve intervention. The ethics committee of Careggi University Hospital approved the study protocol, which conforms to the Declaration of Helsinki, and every patient signed a written informed consent. Follow-up information for the occurrence of death or hospitalization for HF was obtained by clinical visits or telephone interviews over the course of the next two years. Hospital records of all patients were screened for the occurrence of clinical events to confirm the obtained information.

2.2. MitraClip procedure

The standardized MitraClip procedure was performed under general anesthesia to avoid any discomfort due to transesophageal echocardiography monitoring.[8,9] Post-procedural pharmacologic management included a 3-month prescription of clopidogrel 75 mg daily in addition to aspirin or an anticoagulant, as well as optimal HF treatment that is consistent with HF guidelines. Procedural success was defined as a non-complicated placement of $\geq$1 clip coinciding with a peri-procedural estimated MR reduction to $\leq$Grade 2, in accordance with MVARC criteria.[10]

2.3. Echocardiographic evaluation

Serial comprehensive echocardiographic examinations were performed by two trained physicians and reviewed by a third reader, who adjudicated the reported case of disagreement. MR severity was classified according to the American Society of Echocardiography guidelines based upon a validated multi-integrative method.[11] Both qualitative (color flow mapping) and quantitative measurements (proximal isovelocity surface area) were used to grade the MR severity from Grades 0 to 4 (Grade 0: no/trace; Grade 1: mild; Grade 2: moderate; Grade 3: moderate-to-severe; and Grade 4: severe). Systolic pulmonary arterial pressure (PAPs) was obtained from the summation of the trans-tricuspidalis regurgitation gradient and the estimated central venous pressure. Serial LV volumes were calculated using Simpson's biplane method. LV remodeling was assessed by calculating the percentage of volume changes over time (6 months after index procedure volume minus baseline volume). LV reverse remodeling was defined as a decrease in LV end-systolic volume (LVESV) of >15%. LV adverse remodeling was defined as a >10% increase in LVESV. No LV remodeling was defined as a change between −15% and 10% in LVESV.[12,13] An automated measurement tool using speckle tracking was used to obtain global longitudinal strain (GLS, whenever feasible), which reflects the longitudinal contraction of the myocardium from standard three-, four-, and two-chamber apical views, with manual editing of the contours if necessary (EchoPac 8.0, General Electric Medical Systems).

2.4. Statistical analysis

Continuous variables are presented as the mean ± standard deviation. Categorical variables are presented as counts and percentages. Differences in patient characteristics, were compared using an independent−sample t-test (if normally distributed) or Mann-Whitney U-test (if not) for continuous variables, and the Kruskal-Wallis test for non-parametric data when appropriate. Categorical variables were analyzed using χ^2 or Fisher's exact test for categorical variables and the Kruskal-Wallis test for non-parametric data, as appropriate. ANOVA for repeated measurements was carried out for comparisons of LV volume changes for the study subgroups. For the identification of independent factors of reverse LV-R (delta change 6-month LVESV − baseline LVESV, mL), multivariable logistic regression analysis was carried out with step-wise inclusion of the following factors: age, baseline LV EF, baseline LV end-diastolic volume (EDV), baseline LVESV, diabetes mellitus, and previous myocardial infarction. Cumulative event-free survival from all-cause mortality and hospitalization for HF estimates were plotted using the Kaplan−Meier technique. The differences between the survival curves of the reverse and adverse/no LV remodeling patterns were tested with the log-rank test. The Cox proportional hazards model was applied to identify independent predictors of 2-year all-cause mortality and hospitalization for HF, including only variables with $p < 0.10$ in the univariate analysis: age, baseline LVEF, 6-month adverse remodeling pattern, chronic renal failure, diabetes, and previous myocardial infarction. The reliability of LV volumes was assessed using the intraclass correlation coefficient (ICC). Statistical analyses were performed using commercially available software (SPSS, version 26.0, Chicago, IL, USA). A two-sided p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Study population

From September 2017 to August 2019, 47 consecutive patients underwent the MitraClip procedure. A total of two patients were excluded from the study because of an early switch to surgical mitral valve intervention. Thus, 45 patients (28, 62% male) with a mean age of 78.2 ± 8.3 years (Table 1) and a mean effective regurgitant orifice area (EROA) of 0.427 ± 0.056 cm^2 underwent the MitraClip procedure and represented the final study population. The majority of patients had severe functional MR (37, 82%), with

the remaining eight patients having a concomitant presence of both functional and primary mechanisms of MR, the predominant component being the functional one, and were highly symptomatic (NYHA class 3.74 ± 0.44). Study patients were at high surgical risk, as evidenced by a high logistic EuroSCORE (mean 22.41 ± 8.4) and STS PROM (4.6 ± 1.9). At echocardiographic evaluation, patients had depressed left ventricular function [mean LVEF: 36.5 ± 12.8%, mean GLS: −11.5 ± 2.4% (available for 22 patients)]. Impaired renal function was present in 19 patients (42%; mean glomerular filtration rate 46.9 ± 20.9 mL/min). Twenty-six patients (58%) had a history of previous myocardial infarction, 23 (51%) had a history of previous percutaneous coronary angioplasty, 5 (11%) had a history of previous coronary artery bypass grafting, 10 (22%) had chronic obstructive pulmonary disease, 6 (13%) had peripheral artery disease, and 19 (42%) had permanent atrial fibrillation. Patients were treated with standard HF medication: 82% received beta-blockers, 62% received an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, 46% received aldosterone antagonists, and 16% received sacubitril/valsartan. CRT was present in 16%[7] of patients.

3.2. MitraClip procedure and medical management

Percutaneous mitral valve repair with MitraClip was successful in all patients; an average of 1.2 MitraClips was used. Specifically, in our series, the first generation of the MitraClip device, namely NT, was mainly implanted, and a small number of patients received a second MitraClip, according to residual mitral regurgitation degree, post-procedural mitral valve area, and mitral valve gradient. The severity of the MR decreased from a mean grade of 3.6 ± 0.48 to a mean grade of 1.6 ± 0.49 ($P < 0.0001$), and the average mitral valve gradient measured after the procedure was 4.17 ± 1.5 mmHg.During follow-up, medical treatment remained substantially unchanged for all patients: 84% received beta-blockers, 66% received an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, 42% received aldosterone antagonists, and 16% received sacubitril/valsartan, without a significant difference between the reverse and adverse/no remodeling groups (See Table 2). At six months, the average MR was 1.69 ± 0.55 with a MR grade of >2/4 in 2 (4.4%) patients — when LV remodeling would have likely, an upgrade from dual-chamber to biventricular pacing was required in one case. Furthermore, a significant reduction in PAPs from baseline to six months was observed in all patients. Finally, a significant improvement in NYHA functional class from baseline up to 6-month follow-up was observed (1.57 ± 0.58).

3.3. Patterns of ventricular remodeling after MitraClip procedure

Overall, at baseline, 85% of patients showed eccentric LV remodeling. After the MitraClip procedure, the LVEDV and LVESV decreased from baseline to 6-month echo, along with an improvement in LVEF (Table 3).

The average LV remodeling at six months after intervention was −13% ± 16%. Reverse remodeling occurred in 23 patients (51%), no remodeling occurred in 14 (31%), and adverse remodeling occurred in 8 patients (18%). In comparison to reverse remodeling patients, adverse/no remodeling patients were more likely to have a history of previous myocardial infarction and percutaneous coronary intervention, as well as having previously received CRT (Table 1). Both LVEDV and LVESV increased early after the procedure and up to one month and continued to increase progressively from 1–6 months, in patients showing adverse remodeling,

Table 1
Baseline clinical and echocardiographic characteristics.

	All patients (45)	Adverse LV remodeling (n = 8)	No LV remodeling (n = 14)	Adverse-No LV remodeling (n = 22)	Reverse LV remodeling (n = 23)	P-value*
Age, years	78.2 ± 8.3	72.5 ± 12.5	79.9 ± 6.8	77.2 ± 9.7	79.2 ± 6.9	0.084
NYHA IV	73	100	64	77	70	0.999
Male	62	50	78	68	43	0.095
AHT	69	50	64	59	78	0.165
DYSL	42	25	50	41	43	0.862
HUA	18	12	28	23	13	0.396
SMOKE	16	37	0	13	17	0.728
Diabetes	29	37	21	27	30	0.815
COPD	22	25	21	22	22	0.936
PAD	13	0	14	9	17	0.413
CKD	42	50	50	50	35	0.302
Prior MI	58	62	85	77	39	0.010
Prior CABG	11	12	21	18	4	0.140
Prior PCI	51	1	78	77	26	0.001
CAF	42	37	29	32	52	0.167
LBBB	16	25	7	13	17	0.728
PM	20	0	14	9	30	0.074
ICD	24	37	21	27	22	0.666
CRT	16	37	21	27	4	0.034
ECHO variables						
EROA (cm^2)	0.42 ± 0.056	0.39 ± 0.18	0.37 ± 0.26	0.37 ± 0.25	0.47 ± 0.33	0.001
LVEDV (ml)	154.7 ± 63.4	163.9 ± 55.05	167.4 ± 53.08	166.1 ± 52.5	143.8 ± 71.8	0.240
LVESV (ml)	103.5 ± 51.5	115.2 ± 46.1	113.7 ± 45.6	114.3 ± 44.7	93.2 ± 56.4	0.174
LVEF (ml)	36.5 ± 12.7	31.8 ± 10	34.3 ± 12.2	33.4 ± 11.09	39.4 ± 13.04	0.115
SPAP (mmHg)	38.7 ± 10.5	33.6 ± 11.8	37.8 ± 11.6	36.3 ± 11.6	41.1 ± 9.02	0.123
LAA (cm^2)	28.2 ± 7.6	28.1 ± 10.04	27.1 ± 4.3	27.5 ± 6.7	28.9 ± 8.04	0.120

Data are presented as mean ± standard deviation or %. NYHA: New York heart association; AHT: arterial hypertension; COPD: chronic obstructive pulmonary disease; PAD: peripheral artery disease; MI: myocardial infraction CKD: chronic kidney disease; LBBB: left bundle branch block; PM: pacemaker; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; DYSL: dyslipidemia; HUA: hyperuricemia; CABG: coronary artery bypass graft surgery; PCI: prior percutaneous coronary intervention; CAF: chronic atrial fibrillation; EROA: effective regurgitant orifice area; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary artery pressure; and LAA: left atrial area. *: p-values refer to the comparison of 'Adverse-No LV remodeling' vs. 'Reverse LV remodeling'.

Table 2
Changes in medical therapy from baseline to 6 months

	All patients (45)	Adverse LV remodeling (n = 8)	No LV remodeling (n = 14)	Adverse-No LV remodeling (n = 22)	Reverse LV remodeling (n = 23)	P-value*
Medical therapy						
ACEi/ARb (baseline)	62	62	57	59	65	0.424
ACEi/ARb (6-month)	66	75	57	64	70	0.673
ARNI (baseline)	16	25	14	18	13	0.634
ARNI (6-month)	16	25	14	18	13	0.634
Beta-blocker (baseline)	82	88	79	82	78	0.765
Beta-blocker(6-month)	84	88	86	86	78	0.477
MRA (baseline)	46	38	57	50	43	0.661
MRA (6-month)	42	38	50	46	39	0.667

Data are presented as %. ACEi: angiotensin-converting enzyme-inhibitors; ARb: Angiotensin-receptor blockers; ARNI: angiotensin-receptor/neprilysin inhibitor; and MRA: mineralocorticoid-receptor antagonist.*: p-values refer to the comparison of 'Adverse-No LV remodeling' vs. 'Reverse LV remodeling'.

resulting in a worsening of LVEF (see below, Fig. 1 Panel A, B, and C). After 6 months, there was no significant further increase of LV volumes. In contrast, neither LVEDV nor LVESV changed significantly during the follow-up period in patients with no remodeling (Fig. 1 Panel A, B, C). Finally, when compared to adverse/no remodeling patients, in reverse remodeling patients, LV volumes decreased early after the procedure up to one month and continued to decrease progressively and significantly from 1–6 months, resulting in a significant improvement of LVEF at 6 months (Fig. 1 Panels,A,B,C). There were no significant further changes of LV volumes after 6 months.

3.4. Reliability of LV volumes

Intra- and inter-observer reproducibility of LV volumes was assessed in all patients. The intra-observer intra-class correlation coefficients (rho) for LVESV were 0.98 (95% CI = 0.97–0.99) and 0.99 (95% CI 0.993–0.998) for LVEDV, respectively (P < .0001, for both). The inter–observer intra-class correlation coefficients (rho) for LVESV were 0.99 (95% CI = 0.98–0.99) and 0.98 (95% CI 0.97–0.99) for LVEDV, respectively (P < .0001, for both).

3.5. Ventricular remodeling: predictors and clinical outcome

The characteristics of the different LV remodeling patterns are reported in Table 1. There was a clear trend toward less reverse remodeling in patients with larger, but not significant, baseline LVEDV. In a linear multivariable regression model, baseline LVEDV was a strong independent predictor of reverse LV remodeling [β −0.564, 95% CI (−0.363)-(−0.074); P = 0.004], as were age [β −0.386, 95% CI (−2.043)–(−0.233); P = 0.015] and diabetes mellitus [β −0.316, 95% CI (−0.336)–(−0.276); P = 0.047], whereas baseline LVEF [β 0.36, 95% CI (−0.525)–(0.662); P = 0.167] and LVESV were not [β −0.243, 95% CI (−0.258)–(0.26); P = 0.108]. Furthermore, an LVEDV ≤130 mL was strongly associated with reverse remodeling with an OR: 0.796 (CI: 0.052-0.792, P = 0.022). At follow-up (17.5 ± 9.3 months), there were 12 events (26%). Specifically, 6 (13%) deaths occurred: 1 (4.3%) non-cardiac death in reverse LV remodeling for hemorrhagic meningioma, and 5 (23%) cardiac death in adverse/no LV remodeling patients. Furthermore, 6 (13%) hospitalizations for HF occurred, with all 6 (27.3%) in adverse/no remodeling patients. In comparison to reverse LV remodeling patients, the event-free survival curve of patients with adverse/no LV remodeling pattern was lower (77.3% vs. 95.7%, log-rank P value = 0.09), as was the event-free hospitalization curve for HF (72.7% vs. 100%, log-rank P value = 0.031). Furthermore, the event-free survival and hospitalization curve for HF of patients with adverse/no LV remodeling pattern was lower (50% vs. 95.7%, log-rank P value = 0.006) (Fig. 2). In Cox regression analysis, only the adverse remodeling was associated with all-cause mortality and hospitalization for HF, with hazard ratio of 5.6 (95% CI 1.65-19.00, P = 0.006). When adverse and no remodeling patients were combined, the hazard ratio for all-cause mortality and HF was 10.08 (95% CI 1.29–78.6, P = 0.027).

4. Discussion

4.1. Remodeling after MitraClip procedure

The EVEREST trials substudies assessed LV volume changes and showed a 10% average decrease in LVEDV for the subgroup with functional MR and an average 14% decrease for the subgroup with degenerative MR.[14-16] The results of our study are consistent with these findings, showing a high proportion (>50%) of patients with reverse remodeling even in severely diseased hearts. Similarly, high rates of reverse remodeling were observed even after restrictive surgical mitral annuloplasty in ischemic mitral regurgitation.[17] Many factors may contribute to the attenuation of the LV reverse remodeling after the MitraClip procedure, such as the severe baseline dilation of the left ventricle [cut-off values of 65 mm LVEDV[18] or LVEDV <75 mm][19] as well as the magnitude of post-intervention mitral regurgitation.[16] In our study, baseline LVEDV was associated with reverse LV remodeling. Patients with baseline large LVEDV showed a lower reverse remodeling rate. These

Table 3
Changes in mitral regurgitation severity, left ventricular volumes and ejection fraction, left atrial area, and systolic pulmonary artery pressure with echo follow-up.

	Baseline	1 month	6 months	12 months	P value
Mitral regurgitation (0/4)	3.64 ± 0.48	1.49 ± 0.50	1.69 ± 0.55	1.69 ± 0.54	<.0001
LVEDV (mL)	154.7 ± 63.4	149.9 ± 62.3	145.9 ± 60.7	144.1 ± 61.2	.057
LVESV (mL)	103.5 ± 51.5	97.7 ± 49.8	93.6 ± 49.2	92.5 ± 50.5	.009
LVEF (%)	36.5 ± 12.7	38.4 ± 12.9	39.1 ± 13.7	39.2 ± 14.1	.014
LAA (cm^2)	28.2 ± 7.6	27.9 ± 7.6	27.6 ± 7.7	27.8 ± 7.2	.355
SPAP (mmHg)	38.7 ± 10.5	24.6 ± 8.4	23.3 ± 9.6	22.8 ± 8.5	<.0001

Data are reported as median and standard deviation. LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; LAA: left atrial area; and SPAP: systolic pulmonary arterial pressure.

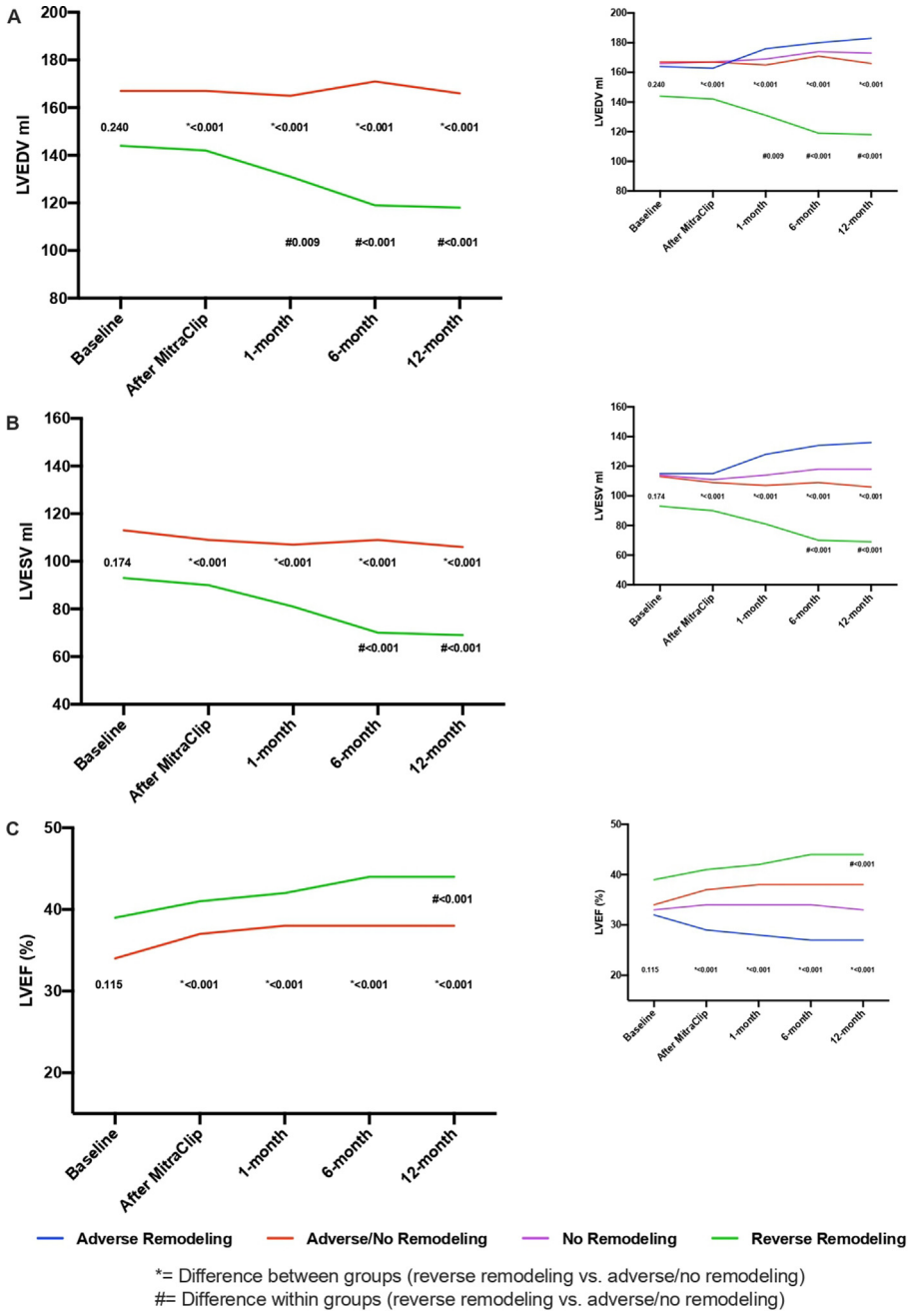

Figure 1. Panels A, B, and C. Time course of left ventricular (LV) end-diastolic volume (LVEDV) (A), LV end-systolic volume (LVESV) (B), and LV ejection fraction (LVEF) (C) according to different LV remodeling patterns. * Difference between groups (reverse vs. adverse/no remodeling); # difference within groups (reverse vs. adverse/no remodeling). Panels in the upper right corners represent patterns of remodeling for all study groups.

findings are not surprising and may be complementary to the apparently opposite results of the MITRA-FR and COAPT trials.[8,9] Consistent with the hypothesis of Grayburn, focused on the relationship between the severity of secondary MR and LV dilation, secondary MR is recognized as proportionate when the regurgitation is appropriate to the LV dilation, and as disproportionate when it is excessive compared to LV dimensions. According to this hypothesis, if meaningful degrees of MR are observed in a patient showing LVEDV in a normal range, the clinical course of the disease can be expected to be primarily determined by the severity of the valvular disease. In contrast, if the LVEDV is out of normal range, the prognosis will be profoundly influenced by the disease process in the left ventricle. In comparison to the COAPT and the MITRA-FR, our patients showed lower large LV volumes and higher EROA (LVEDV: 155 ml versus 194 ml in COAPT and 250 ml in MITRA-FR, and EROA 0.43 cm^2 versus 0.41 cm^2 in the COAPT and 0.31 cm^2 in the MITRA-FR). Taken into account the findings observed in randomized trials and in our registry, we could also hypothesize that if severe MR persists despite maximally tolerated guideline drug medical therapy/CRT as indicated, then MitraClip should be considered prior to irreversible LV dilation, with the need for close monitoring. In the present study, after percutaneous mitral valve correction, the baseline large LVEDV might have attenuated the reverse remodeling. A baseline large LVEDV puts the patient at high risk for developing an afterload mismatch and subsequent impairment of cardiac performance early after mitral valve repair.

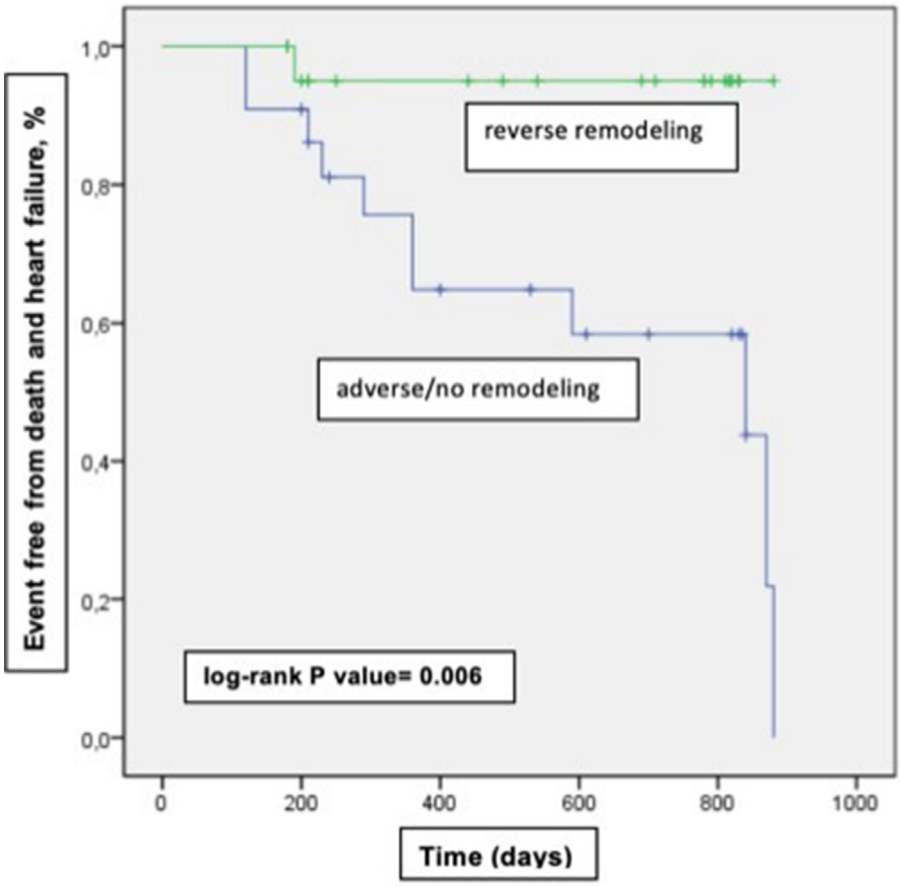

Figure 2. Comparison of event free from all-cause mortality and hospitalization for heart failure between reverse left ventricular (LV) remodeling and adverse/no LV remodeling patients by Kaplan-Meier test (log-rank p = 0.006).

In our study population, although the majority of patients experienced a reduction in LV volumes, there was a subgroup in whom adverse remodeling started early (after the procedure), progressively increased up to six months, and remained unchanged from 6–12 months follow-up period, and this was associated with a high mortality and hospitalization rate for heart failure. This adverse remodeling phenomenon does not appear to be reversible after 12 months of follow-up, if initiated immediately after the MitraClip procedure. Thus, the ability to identify high-risk patients potentially showing a pattern of adverse remodeling before the MitraClip procedure may be of paramount importance in clinical practice in order to avoid the futility of mitral valve intervention. Recently, a post-hoc analysis of MITRA-FR trial found that the degree of mitral regurgitation and the preprocedural LV remodeling had a neutral effect on MitraClip outcomes. This further underscores the need of additional studies to carefully identify the patients with HF and MR, who are most likely to benefit from MitraClip procedure.[20]

4.2. Mechanistic insights and prognostic implication of LV remodeling

The mechanisms explaining the occurrence of adverse LV remodeling after MitraClip implantation are complex and not fully understood. In the study of Grayburn et al,[16] the average LVEF in functional mitral regurgitation patients was 52% (vs. 36.5% in our study population). Nevertheless, LVEF assessment often underestimates cardiac function in the presence of severe MR. In our study, taking into consideration that patients with reverse remodeling compared to those with adverse/no remodeling presented no significant difference in LVEF values, along with the results of multivariate analysis, LVEF, although indicative of poor LV systolic function, was not found to display a prognostic role regarding MitraClip clinical outcomes. Early and persistent adverse remodeling in our study most likely revealed the true severity of underlying myocardial dysfunction. Adverse remodeling has also been linked with higher mortality in other non-valvular interventions, such as post-CRT, post-primary PCI, and post-TAVI.[1-4] In the setting of MitraClip intervention, severe pre-existing LV dysfunction with a limited cardiac reserve is probably the reason for the observed high mortality and HF rate. Likely, a large baseline LVEDV is able to identify MitraClip patients who would not have enough cardiac preload reserve to compensate for the initial effect of the afterload mismatch. It is unknown whether assessment of contractile reserve with low-dose dobutamine or with exercise can better predict the development of adverse remodeling post-MitraClip, but it is worthy of investigation when deciding which patients to treat with mitral valve repair. In the study by Brouwer et al., the PAPs showed moderate value in predicting adverse remodeling.[21] As an expression of combined systolic and diastolic LV dysfunction, the higher PAPs may explain a higher derangement of LV function, which in turn is related to a reduced ability of reverse remodeling. However, in our study, a similar 6-month reduction of PAPs was observed without differences between reverse and adverse/no remodeling patterns. Not surprisingly, in our population, the age and the presence of diabetes mellitus were associated with a reduced probability of reverse LV-R after the MitraClip procedure. It is well known that in elderly patients, the increased interstitial fibrotic tissue content might be related to a

reduced ability to reverse LV-R after myocardial infarction.[22] Moreover, the limited ability of reverse LV-R in diabetic patients in the setting of primary angioplasty for ST-elevation myocardial infarction is well described.[23] Several pathophysiological mechanisms might be involved in the negative association between diabetes and reverse LV-R, including reduced microvascular blood flow, increased myocardial fat and interstitial fibrosis content, advanced glycation end-product deposition, and neurohumoral and autonomic functional changes. Finally, one should realize that although the mechanisms of the adverse/no-remodeling remain to be clarified, monitoring change in LV volumes after MitraClip implantation is recommended because in the case of developing adverse remodeling at six months, the risk of death and HF hospitalization within two years is high. This could be considered as a red flag for the treating physician to further optimize medical HF therapy and/or seek other HF treatments such as CRT, left ventricular assist device, or cardiac transplantation. Accordingly, a non-negligible role of optimization of medical therapy in MitraClip patients was found in the MITRA-FR study at 2 years of follow-up, showing a no-significant trend toward more hospitalization occurring in the medically managed patients.[24] Notably, in our study, the model adopted to evaluate predictors of remodeling might be influenced by the small, simple size; therefore, we recommended caution in interpreting our findings.

4.3. Limitations

The results of this study should be considered in the context of the following limitations: This was a single-center registry and the sample size of the study population included was relatively small. This could have led to a type II error in the interpretation of results. Moreover, the echocardiographic examination has not been reviewed by an independent core laboratory. Thus, caution is needed to extend our findings to different populations. However, all analyses were conducted by skilled and highly experienced physicians utilizing validated methods. For patients who died before 6 months, the last echo available (at 3 months) was considered, which may generate some bias, particularly towards the relationship between LV remodeling and outcome. However, in surviving patients, the evaluation of the LV remodeling extends up to 12 months, adding a small piece to the developmental history of geometrical changes in the left ventricle after percutaneous mitral repair. In addition, the optimization of medical therapy towards follow-up was left to the attending physician. Therefore, the proportion of patients with LV adverse/noremodeling might be different than we have presented. In addition, the relatively small number of patients may have an impact through multivariate analysis of the different risk factors of LV remodeling, and caution is warranted in interpreting our findings. Finally, in our study, baseline LVEF was not a prognostic marker. The limitations of the LVEF as an expression of LV systolic dysfunction are well known. The ability of GLS to detect and quantify subtle disturbances in LV systolic function has been validated by tagged magnetic resonance imaging.[25] However, in our study, the GLS values were available only in 22 patients, and cardiac MRI was not planned before intervention.

5. Conclusions

In our real-world study, one-in-two patients undergoing percutaneous mitral valve repair for severe MR showed reverse remodeling. However, in the other half of patients, there was a sustained adverse and no remodeling, which was associated with subsequently high mortality and hospitalization for HF. Large baseline LV volumes may help us in capturing true severe underlying cardiac systolic dysfunction in order to fine-tune patient selection for the MitraClip procedure. Furthermore, due to the limited sample size, our findings are hypothesis-generating and could serve as the basis for larger confirmatory studies.

Conflict of interest

None declared.

Founding

None.

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