Midterm clinical and echocardiographic results and predictors of mitral regurgitation recurrence following restrictive annuloplasty for ischemic cardiomyopathy

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Objective: Although mitral restrictive annuloplasty plus coronary artery bypass grafting are considered the best therapeutic strategies for ischemic cardiomyopathy with chronic mitral regurgitation, some recurrences are still reported. We evaluated predictors for late recurrence of ischemic cardiomyopathy with chronic mitral regurgitation.

Methods: Hospital outcome and serial clinical and echocardiographic (preoperative, discharge, 6 months, end of follow-up) follow-up assessments were recorded for 82 consecutive patients with ischemic cardiomyopathy with chronic mitral regurgitation having coronary artery bypass grafting + mitral restrictive annuloplasty (2 sizes ring downsizing). Recurrent ischemic cardiomyopathy with chronic mitral regurgitation was defined by grade ≥ 2 at echocardiography.

Results: Hospital mortality was 4.9%; 17.7 ± 1.7 (standard error) months (range 1–55) survival was $95.5\% \pm 2.5\%$. Two-year Kaplan-Meier freedom from reintervention was $94.2\% \pm 4.2\%$; from revascularization, $87.5\% \pm 11.7\%$; from congestive heart failure, $83.8\% \pm 5.7\%$; from ischemic cardiomyopathy with chronic mitral regurgitation grade ≥ 2 , $46.5\% \pm 11.2\%$. Recurrence of ischemic cardiomyopathy with chronic mitral regurgitation gave lower 2-year Kaplan-Meier freedom from death ($P = .03$) and lower 2-year freedom from congestive heart failure ($P = .0001$), reintervention ($P = .034$), and tricuspid insufficiency ($P = .0001$). Ischemic cardiomyopathy with chronic mitral regurgitation recurrence correlated with worsened New York Heart Association class ($P = .0001$), left ventricular ejection fraction ($P = .024$), pulmonary arterial pressures ($P = .0001$), left ventricular end-diastolic diameter ($P = .004$), left ventricular end-systolic diameter ($P = .014$), indexed left ventricular mass ($P = .008$), and coaptation depth ($P = .0001$). Independent predictors for recurrent ischemic cardiomyopathy with chronic mitral regurgitation were previous anterior + posterior myocardial infarction (odds ratio 3.70; confidence interval 2.93–5.41; $P = .001$), preoperative left ventricular end-diastolic diameter ≥ 70 mm (odds ratio 3.91; confidence interval 2.65–5.22; $P = .001$), and coaptation depth at discharge ≥ 0.5 cm (odds ratio 11.9; confidence interval 5.91–21.34; $P = .0001$). Preoperative left ventricular end-diastolic diameter ≥ 70 mm correlated with higher congestive heart failure ($P = .002$), recurrent ischemic cardiomyopathy with chronic mitral regurgitation ($P = .0001$), worsened New York Heart Association class ($P = .0001$), and higher diuretics ($P = .0001$). Coaptation depth < 0.5 cm at discharge accounted for better survival ($P = .010$), lower incidence of congestive heart failure ($P = .0001$), lower need for diuretics ($P = .0001$), and improved New York Heart Association class ($P = .0001$).

Conclusions: Failure of mitral restrictive annuloplasty is responsible for follow-up mortality and congestive heart failure and correlates with absence of cardiac reverse remodeling. Prognosis of patients having mitral restrictive annuloplasty for ischemic cardiomyopathy with chronic mitral regurgitation is good, as long as a low postoperative coaptation depth is achieved. Patients with significant left ventricular dilation should be considered for different surgical strategies.

Different animal and human studies suggested that pathogenesis of ischemic chronic mitral regurgitation (ICMR) is complex and is related to geometrical alterations of the left

ventricle and of the apparatus of the mitral valve (MV).^{1–3} In particular, left ventricular sphericalization, annular enlargement, increased tenting area, and loss of systolic mitral annular contraction all contribute to the development of ICMR.⁴ As ICMR results from multiple mechanisms, current surgical therapy consisting of mitral restrictive annuloplasty (MRA) with an undersized annular ring does not always provide durable repair.⁴

Different preoperative echocardiographic predictors of ICMR recurrence have been described, ranging from ventricular dilation,⁵ high sphericity index,⁶ high interpapillary

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Abbreviations and Acronyms

- AMI = acute myocardial infarction
- CABG = coronary artery bypass grafting
- CD = coaptation depth
- CHF = congestive heart failure
- CPB = cardiopulmonary bypass
- ICMR = ischemic chronic mitral regurgitation
- LAD = left atrial diameter
- LVEDD = left ventricular end-diastolic diameter
- LVEF = left ventricular ejection fraction
- LVESD = left ventricular end-systolic diameter
- LVMi = indexed left ventricular mass
- mean Δp = transmitral mean gradient
- MRA = mitral restrictive annuloplasty
- MV = mitral valve
- NYHA = New York Heart Association
- PAP = systolic pulmonary arterial pressure
- TI = tricuspid insufficiency grading

distance,⁷ coaptation depth (CD) > 10 mm.⁸ All these data suggest that surgery cannot effectively induce reverse remodeling of severely impaired ventricles. Accordingly, recurrence of ICMR has been predominantly related to progressive ventricular remodeling. Similarly, when MRA fails, recurrent episodes of heart failure occur and follow-up morbidity and mortality increase.⁹ However, literature still lacks intraoperative or postoperative indexes anticipating MRA failure.

Therefore, it was the aim of the study to rule out independent predictors of recurrent ICMR following MRA. Echocardiographic and clinical outcomes in patients with successful MRA or with MRA failure were also compared.

MATERIALS AND METHODS

Patients and Surgery

Between August 2004 and February 2008, 84 nonselected consecutive patients admitted because of coronary disease and ICMR, having MRA+ coronary artery bypass grafting (CABG), were enrolled in the study. Our Institutional Review Board approved this study and waived the need for individual consent. All patients had ICMR grade 3+ or 4+ at preoperative echocardiography. Patients demonstrating ICMR grade 2+ had intraoperative provocative testing and were enrolled whenever 3+ to 4+ ICMR was evidenced. ICMR was always due to postinfarction restrictive systolic leaflet motion (Carpentier type IIb), to severe annular dilation because of ischemic dilated cardiomyopathy (Carpentier type I), or to a combination of both (Carpentier type I+IIb; Table 1). Patients with concomitant surgical procedures (apart from tricuspid annuloplasty) were excluded. Accordingly, patients with tricuspid regurgitation grade ≥ 2 or tricuspid regurgitation < 2+ in the presence of dilated tricuspid annulus exceeding 21 mm/m² indexed to body surface area at transthoracic echocardiography always had tricuspid annuloplasty.

All patients had symptoms of heart failure, and the majority presented in New York Heart Association (NYHA) class III or IV (Table 1). Both elective and nonelective patients were enrolled. Mean logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) was 8.3 ± 1.5. Baseline characteristics are presented in Table 1.

TABLE 1. Preoperative and intraoperative data

Variables	No. of patients	% of global population
Age (y)	70.2 ± 3.8	—
Sex (male)	54	65.8
EUROscore	8.3 ± 1.5	—
NYHA class	3.4 ± 0.6	—
Canadian Class Score	3.3 ± 0.8	—
Diabetes	36	43.9
Hypertension	55	67.0
COPD	25	30.5
Left main stem disease	26	31.7
Previous AMI	51	62.2
Recent (<4 wk) AMI	42	51.2
Anterior AMI	10	12.1
Posterior AMI	57	69.5
Anterior+posterior AMI	11	13.4
Emergency	3	3.6
UA/NSTEMI	31	37.8
STEMI	1	1.2
No. CABG	2.4 ± 0.9	—
LITA CABG	82	100
Radial artery CABG	24	29.3
ACC time	73.6 ± 4.5	—
CPB time	126.9 ± 12.2	—
Tricuspid plasty	21	25.6

CABG	Mean flow (mL/min)	Pulsatility index
LITA-to-left anterior descending	38.6 ± 18.2	1.5 ± 1.0
Radial artery	44.7 ± 27.1	1.1 ± 0.9
Saphenous vein	38.4 ± 12.2	1.8 ± 1.1

COPD, Chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; AMI, acute myocardial infarction; UA/NSTEMI, unstable angina/non-ST elevation myocardial infarction; CABG, coronary artery bypass graft; LITA, left internal thoracic artery; ACC, aortic crossclamp; CPB, cardiopulmonary bypass.

Surgery was performed by the same surgeon (A.R.) through a median sternotomy. The ascending aorta was always cannulated, and the venous return was always accomplished through a double caval cannulation. CABG was constructed as already reported.¹⁰ The mitral valve was exposed through longitudinal atriotomy along the Waterston's groove in all patients. Ring size (Carpentier-Edwards Physio ringor Carpentier-McCarthy-Adams ring; both Edwards LifeSciences, Irving, Calif) was determined after measurement of the height of the anterior leaflet and intertrigonal distance, and then downsizing by 2 sizes (ie, size 26 when measuring 30). Complete symmetric rings (Carpentier-Edwards Physio rings) were preferred when ICMR was predominantly due to annular dilation (Carpentier type I), and complete asymmetric rings (Carpentier-McCarthy-Adams rings) were used when inferior or posterolateral infarction caused restrictive systolic leaflet motion (Carpentier type IIb). Tricuspid annuloplasty was always accomplished with a Carpentier Edwards MC3 ring (Edwards Lifesciences). Cardiopulmonary bypass (CPB) was standardized and conducted as already reported.¹⁰

Echocardiography

Echocardiography was always performed by the same 2 cardiologists, blinded toward the surgical technique, using a VIVID 7 Pro ultrasound machine (GE Technologies, Milwaukee, Wis). All patients had transthoracic

echocardiography preoperatively, at hospital discharge, at 6 months' follow-up, and at the end of the follow-up (mean 17.8 ± 15.3 [standard deviation] months; range 1–55 months). Follow-up was closed on March 30, 2008 and was 100% completed.

Transthoracic echocardiographic evaluation consisted of standard echocardiography examination, including grading of the severity of ICMR (semiquantitatively from color-flow Doppler), left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF), indexed left ventricular mass (LVMi), CD, transmitral mean gradient (mean Δp), systolic pulmonary arterial pressure (PAP), and tricuspid insufficiency grading (TI).

All patients also had intraoperative transesophageal echocardiography assessment of left ventricular and valve function. MV repair was considered successful if there was no residual mitral regurgitation following CPB discontinuation, with an adequate preload achieved (central venous pressure between 10 and 15 mm Hg). Recurrence of ICMR was defined as grade $\geq 2/4+$ at semiquantitative color-flow Doppler analysis.

Clinical Assessment and Follow-up

Preoperative clinical status was determined according to the criteria of the NYHA up to 5 days before surgery and was reassessed at discharge, at 6 months, and at the end of follow-up. As a surrogate outcome of heart failure, need and dose of furosemide were assessed at the same time points. Deaths and episodes of acute congestive heart failure (CHF), redo mitral surgery, and re-revascularization (either surgical or percutaneous) during the follow-up were recorded.

Statistical Analysis

All data were prospectively recorded using the institutional database. Statistical analysis was performed by the SPSS program for Windows, version 13.0 (SPSS Inc, Chicago, Ill). Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables are presented as absolute numbers and percentages. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired *t* test, whereas the Mann-Whitney *U* test was used for non-normally distributed variables. Categorical variables were analyzed using either the chi-square test or Fischer exact test. Comparisons between and within groups were made using 2-way analysis of variance for repeated measures. Univariate analyses of risk factors for recurrence of ICMR were performed, calculating odds ratios with 95% confidence intervals. Variables with a *P* value $< .0001$ were consecutively subjected to a multivariate logistic regression model to assess the independent impact of each risk factor on recurrence of ICMR. A stepwise (backward Wald) multivariable binary logistic regression analysis was used to test for predictors of recurrence of ICMR. Both regression model discrimination and calibration were assessed by using the c-statistic for regression model discrimination and the Hosmer-Lemeshow test statistic for model calibration.

Two-year freedoms from death, CHF, hospital readmission, and redo surgery were determined with the method of Kaplan-Meier life table analysis. Log-rank test was performed to ascertain differences between patients with and without ICMR recurrence.

RESULTS

Preoperative and intraoperative data are reported in Table 1.

Intraoperative Mitral Results

During the study period, 2 patients demonstrated persistent intraoperative 1 to 2+ ICMR following CPB despite 2-size undersizing and had valve replacement following

reestablishment of CPB. Therefore, these 2 patients were excluded from the study because of the different surgical therapy. The remaining 82 patients achieved a successful MV repair and were definitively enrolled and followed. Mean mitral ring size was 25.7 ± 1.8 (median size 26; range 24–32). There were no cases of systolic anterior motion or significant mitral stenosis (mean transvalvular gradient 4.5 ± 0.5 mm Hg; mean MV area 2.7 ± 1.0 cm²). Twenty-nine patients (35.3%) had tricuspid annuloplasty. Transit-time flowmetry demonstrated good values in all CABG (Table 1).

Hospital Outcome

Hospital mortality was 4.9% (4 patients). There were 1 perioperative acute myocardial infarction (AMI; 1.2%) and 5 postoperative low output state (6.1%) requiring prolonged intra-aortic balloon pump (>48 hours) and inotropic support with intravenous dobutamine and levosimendan; transient paroxysmal atrial fibrillation requiring intravenous amiodarone developed in 18 patients (21.9%). Three patients (3.6%) experienced respiratory failure because of pneumonia, acute renal failure requiring renal replacement therapy with continuous venovenous hemofiltration developed in 2 patients (2.4%), and cognitive dysfunction developed in 1 patient (1.2%). Overall hospital morbidity accounted for 22 patients (26.8%). Intensive care stay was 43.4 ± 9.1 hours (range 28–84 hours); hospital stay was 6.7 ± 2.4 days. However, excluding the 4 patients who died, all other patients completely recovered and were discharged in healthy conditions.

Follow-up Clinical Outcome

Mean follow-up was 17.8 ± 1.7 (standard error) months (range 1–55 months). Three patients died during follow-up because of acute CHF ($n = 2$) and sudden death ($n = 1$). Both patients who died of CHF showed recurrence of ICMR at follow-up. Therefore, the 2-year Kaplan-Meier freedom from death was $96.5\% \pm 2.5\%$ (Figure 1, A). CHF developed in 9 patients during follow-up (2-year actuarial freedom from CHF $83.0\% \pm 5.7\%$; Figure 1, B), 2 patients needed redo mitral surgery (2-year actuarial freedom from mitral reintervention $94.2\% \pm 4.2\%$; Figure 1, C), and 1 patient had re-revascularization (2-year actuarial freedom from re-revascularization $87.5\% \pm 11.7\%$).

Twenty patients (25.6%) of 78 discharged from the hospital had recurrent ICMR (grade ≥ 2) at echocardiographic follow-up, resulting in a 2-year actuarial freedom from ICMR of $46.5\% \pm 11.2\%$ (Figure 1, D). However, when patients with recurrent ICMR were compared with those without ICMR, a significantly lower 2-year freedom from death (log-rank *P* = .0001; Figure 2, A), from CHF (log-rank *P* = .030; Figure 2, B), and from redo mitral surgery (*P* = .034; Figure 2, C) was demonstrated. Moreover, a significant proportion of patients with preoperative severe

FIGURE 1. Actuarial survival (A) and freedom from congestive heart failure (B), redo mitral surgery (C), re-revascularization (D).

systolic impairment (LVEF <25%; 8 patients [9.7% of the population]) had recurrent ICMR following surgery (recurrent ICMR 6/20 [30.0%] vs no recurrent ICMR 2/62 [3.2%]; $P = .002$).

When functional status was considered, despite the fact that both groups of patients (those with recurrent ICMR or not) improved their NYHA class, those without ICMR during follow-up showed a significantly better recovery of NYHA class, together with a significantly lower need for diuretics (Table 2). Accordingly, recurrent ICMR induced progressive increase of the daily furosemide during the follow-up (Table 2).

Echocardiographic Results

A completely different pattern of left and right ventricular echocardiographic results was found in patients with recurrent ICMR and those without ICMR. In particular, patients with recurrent ICMR showed absence of reverse remodeling of LVEDD, LVESD, and LVMI, with a slight augmentation of LAD (Table 3). Accordingly, LVEF did not improve during the follow-up despite revascularization. TI grade and PAP did not decrease despite MRA-reduced ICMR

(Table 3). MRA might have mimicked iatrogenic mild stenosis, given the slight augmentation of the transmitral mean Δp . Finally, after a significant amelioration of mitral CD at discharge, CD increased parallel to the worsening of ICMR, transmitral mean Δp progressive reduced, and PAP and TI worsened (Table 3).

On the other hand, patients without recurrent ICMR during the follow-up correlated with a significant reverse remodeling of LVEDD, LVESD, LVMI, together with the improvement of LVEF (Table 3). These same patients demonstrated persistently shortened CD from discharge to the end of follow-up and showed a higher mean Δp (compared with patients with recurrent ICMR), with absence of LAD reverse remodeling (Table 3). In this group of patients, TI grade and PAP were reduced in parallel (Table 3).

Predictors of MRA Failure

Univariate analysis revealed that 23 of 45 recorded variables had a significant ($P < .05$) association with recurrence of ICMR during the follow-up (see Appendix). Stepwise logistic regression analysis revealed 3 variables as independent predictors of ICMR recurrence: previous

FIGURE 2. Survival (A), freedom from congestive heart failure (B), and mitral reintervention (C) between patients with ischemic chronic mitral regurgitation recurrence and those without ischemic chronic mitral regurgitation recurrence.

anterior + posterior myocardial infarction (odds ratio 3.70), preoperative LVEDD ≥ 70 mm (odds ratio 3.91), and CD at discharge ≥ 0.5 cm (odds ratio 11.9; Table 4). The discrimination

c-statistic for the final logistic regression analysis was 0.950, suggesting that about 95% of the time, the model predicted a correct response given a set of positive predictor variables. The chi-square test result for the Hosmer-Lemeshow test was 5.11 with 7 degrees of freedom, for an overall chi-square significance of 0.646.

Stratification According to Postoperative CD < 0.5 cm and LVEDD ≥ 70 mm

Subgroup analysis of patients stratified according to discharge CD ≥ 0.5 cm or CD < 0.5 cm revealed significant differences in terms of major clinical end points. In particular, patients with CD < 0.5 cm at discharge showed better survival

(log-rank $P = .010$; Figure 3, A) and higher 2-year freedom from CHF (log-rank $P = .0001$; Figure 3, B). Accordingly, patients with CD < 0.5 cm demonstrated significantly better NYHA class during the postoperative and follow-up time-course (between-groups $P = .0001$), with lower need for daily furosemide (between-groups $P = .0001$; Table 5).

Similarly, when patients were dichotomized according to the preoperative left ventricular dilation, those with preoperative LVEDD ≥ 70 mm showed a significantly lower 2-year freedom from recurrent ICMR ($10.3\% \pm 9.4\%$ vs LVEDD < 70 mm $77.3\% \pm 13.1\%$; $P = .0001$), with lower 2-year freedom from CHF ($53.9\% \pm 15.6\%$ vs LVEDD < 70 mm $94.1\% \pm 3.3\%$, $P = .002$). Furthermore, LVEDD ≥ 70 mm correlated with a progressive worsening of NYHA class during the follow-up (between-groups $P = .0001$), which paralleled a progressive increase of the daily diuretic dose (between-groups $P = .0001$, Table 5).

TABLE 2. Recovery of NYHA class and need for daily dose of diuretics in patients with and without ICMR recurrence

	Preoperative NYHA	Discharge NYHA	6-mo NYHA	Follow-up NYHA	P^*	$P^\dagger$
ICMR	3.7 $\pm$ 0.4	1.8 $\pm$ 0.3	2.1 $\pm$ 0.6	2.6 $\pm$ 0.7	.0001	.0001
No ICMR	3.2 $\pm$ 0.5	1.5 $\pm$ 0.5	1.3 $\pm$ 0.4	1.0 $\pm$ 0.1	.0001	
	Preoperative daily furosemide (mg)	Discharge daily furosemide (mg)	6-mo daily furosemide (mg)	Follow-up daily furosemide (mg)	P^*	$P^\dagger$
ICMR	92.2 $\pm$ 45.7	42.3 $\pm$ 13.6	59.4 $\pm$ 28.4	82.1 $\pm$ 28.5	.05	.0001
No ICMR	71.5 $\pm$ 23.4	25.5 $\pm$ 14.2	20.2 $\pm$ 11.2	13.2 $\pm$ 8.5	.0001	

ICMR, Ischemic chronic mitral regurgitation; NYHA, New York Heart Association. *Statistical probability within group; † statistical probability between groups.

TABLE 3. Echocardiographic results

	Preoperative ICMR	Discharge ICMR	6-mo ICMR	Follow-up ICMR	P*	P†
ICMR	3.5 ± 0.6	1.2 ± 0.4	1.8 ± 0.4	2.5 ± 0.5	.209	.0001
No ICMR	3.4 ± 0.5	0.7 ± 0.4	0.6 ± 0.4	0.5 ± 0.5	.0001	
	Preoperative LAD	Discharge LAD	6-mo LAD	Follow-up LAD	P*	P†
ICMR	46.1 ± 5.7	46.3 ± 5.9	46.9 ± 5.5	46.1 ± 10.6	.301	.101
No ICMR	45.6 ± 3.4	45.5 ± 3.2	44.7 ± 3.6	44.3 ± 3.8	.063	
	Preoperative LVEDD	Discharge LVEDD	6-mo LVEDD	Follow-up LVEDD	P*	P†
ICMR	67.1 ± 8.2	67.0 ± 8.0	67.6 ± 8.2	67.7 ± 8.0	.282	.004
No ICMR	63.9 ± 4.9	62.4 ± 4.9	61.4 ± 4.8	60.5 ± 5.2	.0001	
	Preoperative LVESD	Discharge LVESD	6-mo LVESD	Follow-up LVESD	P*	P†
ICMR	55.3 ± 13.5	55.3 ± 13.0	55.3 ± 13.6	55.4 ± 13.3	.773	.014
No ICMR	54.4 ± 6.6	49.6 ± 6.6	48.1 ± 6.4	46.8 ± 5.9	.0001	
	Preoperative LVMi	Discharge LVMi	6-mo LVMi	Follow-up LVMi	P*	P†
ICMR	145.3 ± 19.2	145.4 ± 19.5	145.8 ± 20.2	146.2 ± 19.1	.089	.008
No ICMR	138.7 ± 20.2	138.5 ± 19.9	136.2 ± 19.6	134.6 ± 19.3	.002	
	Preoperative LVEF	Discharge LVEF	6-mo LVEF	Follow-up LVEF	P*	P†
ICMR	38.1 ± 8.7	35.2 ± 8.0	36.1 ± 9.7	36.3 ± 8.9	.713	.024
No ICMR	40.1 ± 6.8	37.8 ± 6.9	42.7 ± 6.8	44.9 ± 7.2	.0001	
	Preoperative CD	Discharge CD	6-mo CD	Follow-up CD	P*	P†
ICMR	1.3 ± 0.2	0.7 ± 0.3	0.8 ± 0.4	0.8 ± 0.4	.001	.0001
No ICMR	1.3 ± 0.2	0.4 ± 0.2	0.4 ± 0.1	0.5 ± 0.2	.0001	
	Preoperative mean Δp	Discharge mean Δp	6-mo mean Δp	Follow-up mean Δp	P*	P†
ICMR	0.9 ± 0.9	4.7 ± 0.9	4.3 ± 0.8	3.9 ± 1.1	.001	.0001
No ICMR	0.9 ± 0.8	5.6 ± 1.3	5.7 ± 1.2	5.8 ± 1.3	.0001	
	Preoperative TI	Discharge TI	6-mo TI	Follow-up TI	P*	P†
ICMR	2.1 ± 0.6	1.3 ± 0.5	1.5 ± 0.6	2.0 ± 0.7	.544	.0001
No ICMR	1.9 ± 0.5	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.4	.0001	
	Preoperative PAP	Discharge PAP	6-mo PAP	Follow-up PAP	P*	P†
ICMR	45.0 ± 8.4	36.6 ± 7.9	39.1 ± 8.7	38.6 ± 10.2	.110	.0001
No ICMR	38.1 ± 6.4	31.3 ± 5.9	29.6 ± 5.5	28.8 ± 5.6	.0001	

ICMR, Ischemic chronic mitral regurgitation; LAD, left atrial diameter; LVEDD, left ventricular diastolic diameter; LVESD, left ventricular systolic diameter; LVMi, left ventricular mass index; LVEF, left ventricular ejection fraction; CD, coaptation depth; Δp, pressure gradient; TI, tricuspid insufficiency; PAP, pulmonary arterial pressure systolic. *Statistical probability within group; †statistical probability between groups.

DISCUSSION

ICMR is considered a common cause of post-AMI congestive heart failure, and it is present in 10% to 20% of patients with coronary artery disease.¹¹ Moreover, it has been considered one of the few targets for therapeutic opportunities in heart failure.¹¹ According to the complex and different pathogenetic mechanisms underlying such disease, a number of different surgical techniques have been developed for ICMR.^{1-4,11} Of all the procedures described, MRA proved to be effective, safe, and reproducible.^{5-9,11} However, all these experiences reported some recurrences, ranging from 15% to 30%, because of a different population profile and follow-up.^{5,7,8,11} In our series, 20 patients (25.6%) had MRA failure during follow-up, in line with other reports. Moreover, a recent article, examining 585

patients over a 17-year period, found that recurrences developed in 28% of patients at 6 months.¹²

The main cause of early failure seems consequential to the action of MRA only at the annular level, whereas it does not fully address the ventricular causes of ICMR.^{11,12} Therefore,

TABLE 4. Independent predictors of recurrence of ICMR analyzed by multivariate logistic regression analysis

Variables	Odds ratio	Confidence limit (95%)	P
Anterior + posterior AMI	3.70	2.93–5.41	.001
Preoperative LVEDD ≥ 70 mm	3.91	2.65–5.22	.001
CD at discharge ≥ 0.5 cm	11.9	5.91–21.34	.0001

ICMR, Ischemic chronic mitral regurgitation; AMI, acute myocardial infarction; LVEDD, left ventricular end-diastolic diameter; CD, coaptation depth.

FIGURE 3. Survival (A) and freedom from congestive heart failure (B) between patients with coaptation depth ≥ 0.5 cm at discharge and those with coaptation depth < 0.5 cm at discharge.

the progressive ventricular dilation and the ongoing cardiomyopathy act for late recurrences during the follow-up.^{5-8,13} All these factors have led surgeons to identify the predictors for recurrence of ICMR despite MRA. Most of these predictors are preoperative characteristics, such as CD > 10 mm,⁸ preoperative LVEDD > 65 mm,¹⁴ short posterior tethering,¹⁵ and interpapillary distance > 20 mm.⁷ However, literature lacks early predictors of ICMR recurrence following MRA. Our data confirm previous reports¹⁴ showing preoperative enlarged LVEDD (≥ 70 mm in our experience) to predict MRA failure. Accordingly, preoperative LVEDD ≥ 70 mm correlated with lower 2-year freedom from CHF and worsened NYHA class. Moreover, we further found that CD ≥ 0.5 cm at discharge predicted the recurrence of ICMR. Therefore, the identification of a CD ≥ 0.5 cm may help early detection of a higher risk for recurrences. This finding therefore should lead physicians to be more aggressive with medical therapy, to be closer on patient's follow-up, or to consider different strategies.⁵ In our experience, CD ≥ 0.5 cm is the most powerful predictor of recurrent ICMR despite MRA. Furthermore,

compared with the preoperative predictors of ICMR already reported,^{7,8,14,15} CD at discharge is certainly related to the preoperative degree of postischemic left ventricular sphericalization,^{1,2,4} but it may also reflect a slightly less stringent septolateral cinching during the surgical time.¹⁶ Furthermore, dichotomizing patients on the basis of their discharge CD, we found that those with CD ≥ 0.5 cm had poorer survival and lower 2-year freedom from CHF, with worsening NYHA class and progressive decompensation. Accordingly, they needed also higher doses of daily furosemide.

It is well known that patients with ICMR have a worse natural history: the SAVE study demonstrated that patients with mild ICMR had an increased risk of cardiovascular mortality (29% vs 12%) and heart failure (24% vs 16%) at 3.5 years after AMI compared with patients without ICMR. Adjustment for differences in baseline characteristics revealed that mild to moderate ICMR strongly predicted mid-term mortality.¹⁷ Therefore, it was not surprising that patients with recurrent ICMR showed lower 2-year freedom from death, CHF, and redo mitral surgery, together with

TABLE 5. Recovery of NYHA class and need for daily diuretic dose in patients with and without preoperative LVEDD ≥ 70 mm or with and without CD ≥ 0.5 cm at discharge

	Preoperative NYHA	Discharge NYHA	6-mo NYHA	Follow-up NYHA	P*	P†
Preoperative LVEDD ≥ 70 mm	3.6 $\pm$ 0.5	1.8 $\pm$ 0.4	1.9 $\pm$ 0.6	2.4 $\pm$ 1.0	.005	.0001
Preoperative LVEDD < 70 mm	3.3 $\pm$ 0.6	1.6 $\pm$ 0.5	1.5 $\pm$ 0.6	1.1 $\pm$ 0.5	.0001	
	Preoperative daily furosemide (mg)	Discharge daily furosemide (mg)	6-mo daily furosemide (mg)	Follow-up daily furosemide (mg)	P*	P†
Preoperative LVEDD ≥ 70 mm	93.9 $\pm$ 51.6	37.5 $\pm$ 16.8	53.1 $\pm$ 32.9	72.9 $\pm$ 37.6	.007	.0001
Preoperative LVEDD < 70 mm	73.9 $\pm$ 25.7	30.9 $\pm$ 11.7	24.2 $\pm$ 13.8	20.9 $\pm$ 20.7	.0001	
	Preoperative NYHA	Discharge NYHA	6-mo NYHA	Follow-up NYHA	P*	P†
Discharge CD ≥ 0.5 cm	3.6 $\pm$ 0.5	1.8 $\pm$ 0.4	1.9 $\pm$ 0.7	2.3 $\pm$ 0.9	.002	.0001
Discharge CD < 0.5 cm	3.3 $\pm$ 0.5	1.6 $\pm$ 0.5	1.4 $\pm$ 0.4	1.1 $\pm$ 0.4	.0001	
	Preoperative daily furosemide (mg)	Discharge daily furosemide (mg)	6-mo daily furosemide (mg)	Follow-up daily furosemide (mg)	P*	P†
Discharge CD ≥ 0.5 cm	91.6 $\pm$ 49.7	38.3 $\pm$ 15.9	55.0 $\pm$ 30.2	72.5 $\pm$ 37.2	.001	.0001
Discharge CD < 0.5 cm	74.4 $\pm$ 25.3	30.2 $\pm$ 11.3	21.5 $\pm$ 8.7	17.4 $\pm$ 13.4	.0001	

CD, Coaptation depth; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association. *Statistical probability within group; †statistical probability between groups.

a progressive worsening of their NYHA class and need for diuretics, when compared with patients with recurrent ICMR. Given the higher prevalence of recurrent ICMR when high CD is found, patients with discharge CD ≥ 0.5 share the same outcome. Our findings correlated with those of De Bonis¹⁸ showing a significantly worse NYHA class when ICMR recurred and those of Gelsomino,⁶ who found higher NYHA class and reoperation rate when MRA failed. Accordingly, Braun and colleagues¹⁴ showed that recurrent ICMR reduces survival without ventricular reverse remodeling.

When echocardiographic results are considered, we found a different fate of the left ventricle, based on the midterm efficacy of MRA. Failed MRA resulted in recurrent ICMR and therefore did not correlate with any left ventricular reverse remodeling. On the contrary, successful MRA cured ICMR, correlating with reverse remodeling of LVEDD, LVESD, LVMi, together with improved LVEF and right ventricular function, as demonstrated by the amelioration of TI grade and PAP. Therefore, it was not surprising that patients with recurrent ICMR showed worsening functional class and a need for higher daily doses of diuretics. These data agree with the majority of the literature reports, all showing worsened survival and functional deterioration when ICMR recurred.^{5-8,11-13} In fact, it is noteworthy that Bolling and associates¹⁹ first reported NYHA class amelioration following MRA in old ischemic patients in the early 1990s. Since then, recurrences of mitral regurgitation dramatically impacted follow-up survival, despite continuous improvements of the surgical and medical therapies.²⁰ Bax and coworkers²¹ already demonstrated that effective MRA induced left ventricular and left atrial reverse remodeling. Our data confirm those of Bax and colleagues only when left ventricular remodeling was considered. However, we did not find reverse remodeling of the left atrial chamber, even in patients without recurrent ICMR. These results could possibly be related to the higher mean transmitral gradients of patients with successful MRA compared with those with MRA failure. Accordingly, a recent report from Magne and associates²² reported MRA to have the potential to induce variable degrees of iatrogenic functional mitral stenosis. Certainly, more studies addressing such topics are needed to clarify the potential deleterious effects of MRA. Finally, we found that combined anterior + posterior myocardial infarction also predicted midterm failure of MRA. It has been established that evolution of ICMR involves complex interactions between leaflets, annulus, chordae tendineae, papillary muscles, and so on.^{1,2,11} Complex phenomena contributed to ICMR, ranging from posterior papillary muscle dislodgement, anterior and posterior annular dilation, loss of the saddle shape and systodiastolic movements of the annular plane, chordal and papillary muscle tethering action on both leaflets, and so on.²³ Lateral displacement of the posterior papillary muscle appears to play a major role in the development of ICMR following inferior AMI.²³ Small infarcts

in the area of posterior papillary muscle can lead to significant ICMR.²⁴ However, from a functional point of view, it has been demonstrated that the degree of functional mitral regurgitation is determined by mitral tenting, which is directly related to the displacement of the papillary muscles.²⁵ In particular, not only posterior but also apical displacements of both anterior and posterior papillary muscles enhance ICMR.^{11,25} Similarly, left ventricular distortion and remodeling after an anterior infarction displace papillary muscles toward the apex, resulting in apical mitral tethering and restriction of coaptation during systole.²⁶ Moreover, left ventricular restoration in patients with dyskinetic or aneurysmatic left ventricles may often restore the mitral competence.²⁶ Therefore, it is not surprising that patients with either anterior or posterior AMI during their lives had extended and complex preoperative ventricular remodeling. In these patients, further surgical strategies other than MRA should be considered to completely address the complex pathogenesis underlying their ICMR.

Therefore, we conclude that MRA failure is responsible for follow-up mortality and CHF and correlates with the absence of reverse remodeling of the ventricular chamber. Prognosis of patients having MRA in ICMR is good, as long as a low postoperative CD is achieved. Patients with preoperative significant left ventricular dilation exceeding 70 mm of LVEDD or with extensive preoperative left ventricular remodeling because of multiple anterior and posterior infarcts should be considered for complementary surgical strategies.

Limitations of the Study

The main limitation of the study is the small sample size of patients enrolled. This results from the single-center design of the study, which, on the other hand, guarantees uniformity of the surgical technique and perioperative care. The 100% follow-up is also a strength. Another limitation is the relatively low number of recurrent ICMR during the follow-up, which may limit the efficacy of a multivariable analysis, where an accepted rule of thumb is to include 1 variable for consideration for every 10 outcomes of interest. However, we have tried to limit the risk of an overfitted model by including in the logistic regression only those variables ($n=8$) with a highly significant correlation ($P < .0001$) with recurrent ICMR. In this way, the multivariable model proved reliable, given a c-statistic of 0.950 and a Hosmer-Lemeshow's goodness-of-fit P of .646.

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APPENDIX. Perioperative variables analyzed as univariate predictors of ICMR recurrence

Variables	ICMR recurrence	No ICMR recurrence	P
Age	69.9 ± 2.8	70.9 ± 4.0	.711
EUROscore	8.1 ± 1.2	8.3 ± 1.6	.522
Sex (male)	13 (65.0%)	41 (71.9%)	.376
Diabetes	16 (80.0%)	20 (35.1%)	.001
Hypertension	15 (75.0%)	39 (68.4%)	.401
Dyslipidemia	5 (25.0%)	15 (26.3%)	.580
COPD	8 (40.0%)	17 (29.8%)	.285
UA/NSTEMI	10 (50.0%)	21 (36.8%)	.221
STEMI	0 (0%)	1 (1.8%)	.740
Previous AMI	11 (55.0%)	39 (68.4%)	.208
Recent AMI	17 (85.0%)	25 (43.9%)	.001
Anterior AMI	5 (25.0%)	5 (8.8%)	.075
Posterior AMI	6 (30.0%)	51 (89.4%)	.0001
Anterior + posterior AMI	9 (45.0%)	2 (3.6%)	.0001
LMSD	10 (50.0%)	16 (27.6%)	.061
Preoperative NYHA	3.7 ± 0.4	3.2 ± 0.5	.0001
Preoperative diuretics	92.2 ± 45.7	71.5 ± 23.4	.022
Preoperative ICMR	3.5 ± 0.6	3.4 ± 0.5	.037
Preoperative TI	2.1 ± 0.6	1.9 ± 0.5	.441
Preoperative PAP	45.0 ± 8.4	38.1 ± 6.4	.047
Preoperative LAD	46.1 ± 5.7	45.6 ± 3.4	.202
Preoperative LVEDD	67.1 ± 8.2	63.9 ± 4.9	.008
Preoperative LVEDD > 70 mm	14 (73.7%)	4 (7.0%)	.0001
Preoperative LVESD	55.3 ± 13.5	54.4 ± 6.6	.028
Preoperative LVMI	145.3 ± 19.2	138.7 ± 20.2	.069
Preoperative LVEF	38.1 ± 8.7	40.1 ± 6.8	.174

APPENDIX. Continued

Variables	ICMR recurrence	No ICMR recurrence	P
Preoperative CD	1.3 ± 0.2	1.3 ± 0.2	.501
Preoperative transmitral Δp	0.9 ± 0.9	0.9 ± 0.8	.693
No. CABG	2.0 ± 1.1	2.5 ± 0.9	.040
Tricuspid plasty	3 (15.0%)	13 (22.8%)	.348
ACC time (min)	73.4 ± 4.8	73.7 ± 4.5	.832
CPB time (min)	138.7 ± 15.7	136.3 ± 10.8	.450
Discharge NYHA	1.8 ± 0.3	1.5 ± 0.5	.031
Discharge diuretics	42.3 ± 13.6	25.5 ± 14.2	.004
Discharge ICMR	1.2 ± 0.4	0.7 ± 0.4	.0001
Discharge TI	1.3 ± 0.5	1.1 ± 0.2	.533
Discharge PAP	36.6 ± 7.9	31.3 ± 5.9	.025
Discharge LAD	46.3 ± 5.9	45.5 ± 3.2	.063
Discharge LVEDD	67.0 ± 8.0	62.4 ± 4.9	.001
Discharge LVESD	55.3 ± 13.0	49.6 ± 6.6	.010
Discharge LVMI	145.4 ± 19.5	138.5 ± 19.9	.050
Discharge LVEF	35.2 ± 8.0	37.8 ± 6.9	.048
Discharge CD	0.7 ± 0.3	0.4 ± 0.2	.0001
Discharge CD ≥ 0.5 cm	18 (90.0%)	3 (5.3%)	.0001
Discharge transmitral Δp	4.7 ± 0.9	5.6 ± 1.3	.0001
Redo mitral surgery	2 (10.0%)	0 (0%)	.065
Re-revascularization	0 (0%)	1 (1.8%)	.740

COPD, Chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; UA/NSTEMI, unstable angina/non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; AMI, acute myocardial infarction; LMSD, left main stem disease; NYHA, New York Heart Association; ICMR, chronic mitral regurgitation; TI, tricuspid insufficiency; PAP, systolic pulmonary arterial pressure; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVMI, indexed left ventricular mass; LVEF, left ventricular ejection fraction; CD, coaptation depth; CABG, coronary artery bypass grafting; ACC, aortic crossclamp; CPB, cardiopulmonary bypass.