Determinants of functional capacity after mitral valve annuloplasty or replacement for ischemic mitral regurgitation

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ABSTRACT

Objective: To identify the exercise echocardiographic determinants of long-term functional capacity, in patients with chronic ischemic mitral regurgitation, after restrictive mitral valve annuloplasty (RMA) or mitral valve replacement (MVR).

Methods: We retrospectively analyzed 121 patients with significant chronic ischemic mitral regurgitation, who underwent RMA (n = 62) or MVR (n = 59), between 2005 and 2011. Preoperatively, all patients underwent a resting echocardiographic examination, and a 6-minute walking test (6-MWT) to measure distance. Resting and exercise stress echocardiography, and the 6-MWT were repeated at 41 ± 16.5 months.

Results: After surgery, the 6-MWT distance significantly improved in the MVR group, and decreased in the RMA group (+37 ± 39 m vs -24 ± 49 m, respectively; $P < .0001$). Exercise indexed effective orifice area was significantly higher in the MVR, versus the RMA, group (MVR: change from $1.3 \pm 0.2 \text{ cm}^2/\text{m}^2$ to $1.5 \pm 0.3 \text{ cm}^2/\text{m}^2$; RMA: change from $1.1 \pm 0.3 \text{ cm}^2/\text{m}^2$ to $1.2 \pm 0.3 \text{ cm}^2/\text{m}^2$; $P = .001$). The mean mitral gradients significantly increased from rest to exercise, in both groups, but to a greater extent in the RMA group (change from 4.4 ± 1.4 to $11 \pm 3.6 \text{ mm Hg}$; MVR: change from 4.3 ± 1.8 to $9 \pm 3.5 \text{ mm Hg}$; $P = .006$). On multivariate analysis, MVR and exercise indexed effective orifice area were the main independent determinants of postoperative 6-MWT. In the RMA group, 25 patients experienced late mitral regurgitation recurrence, severe in 9 (14%) of them. The rate of postoperative cardiovascular events was significantly higher in the RMA group (21% vs MVR: 8%; $P = .03$). Follow-up survival was 83% in the RMA group and 88% in the MVR group ($P = .54$).

Conclusions: For chronic ischemic mitral regurgitation, MVR versus RMA was associated with better postoperative exercise hemodynamic performance and long-term functional capacity. (J Thorac Cardiovasc Surg 2015;149:1595-603)

The figure shows the 6-minute walking-test distance, in the whole cohort, and according to the surgical treatment: restrictive mitral valve annuloplasty versus mitral valve replacement.

Central Message

Mitral valve replacement for ischemic regurgitation provides better hemodynamic performance and functional capacity, compared with restrictive annuloplasty.

Perspective

For treatment of ischemic mitral regurgitation, controversy persists regarding the superiority of mitral valve annuloplasty versus replacement. Procedures aiming to restore ventricular geometry or targeting subvalvular mechanisms seem promising, but they require further scientific evidence. Mitral valve replacement provides better long-term hemodynamic performance and functional capacity for patients, during exercise, compared with restrictive annuloplasty. Pending further insight from the ongoing Cardiothoracic Surgical Trials Network, valve replacement with preservation of subvalvular apparatus may be a reliable option.

See Editorial Commentary page 1604.

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Chronic ischemic mitral regurgitation (CIMR) is a frequent complication of coronary artery disease and is independently associated with excess mortality and poor outcome.¹⁻³ Restrictive mitral valve annuloplasty (RMA) and mitral valve replacement (MVR) are the most common surgical options for the treatment of CIMR. However, controversy persists regarding the optimal surgical treatment.⁴⁻⁸

Recent results from the Cardiothoracic Surgical Trials Network⁹ showed that patient outcomes with replacement versus repair are similar at 1 year. A previous study showed

Abbreviations and Acronyms

CIMR	= chronic ischemic mitral regurgitation
ESE	= exercise stress echocardiography
MVR	= mitral valve replacement
RMA	= restrictive mitral valve annuloplasty
6-MWT	= 6-minute walking test

that patients treated with RMA for CIMR may develop functional mitral stenosis, both at rest and during exercise, with decreasing functional capacity.¹⁰ In line with these findings, we have reported, using exercise stress echocardiography (ESE), worse hemodynamic performance in patients treated with RMA, compared with MVR.¹¹

The distance required for a 6-minute walking test (6-MWT) provides a good measure of functional capacity and is an adequate alternative to cardiopulmonary testing.^{12,13} This test, coupled with ESE,^{14,15} can accurately assess daily life activities and the real consequences of the underlying disease, in a large group of patients with heart failure of any etiology, and provide important diagnostic and prognostic information. The aim of the present study was to predict the determinants of long-term functional capacity, in patients with CIMR, treated with either RMA or MVR.

METHODS**Population**

We retrospectively analyzed data from 208 consecutive patients who had CIMR, and who underwent either RMA or MVR, combined with coronary bypass surgery, in our institution, between 2005 and 2011. The presence of CIMR was defined by echocardiographic and coronary angiographic findings, using the following criteria: (1) mitral regurgitation >1 week after myocardial infarction; (2) ≥ 1 left ventricular, segmental wall motion abnormalities; (3) significant coronary artery disease ($\geq 75\%$ stenosis of ≥ 1 coronary vessel) in the area creating the wall motion abnormality; (4) structurally normal mitral valve leaflets and chordae tendinae; and (5) type III B Carpentier classification, with or without annular dilatation.¹⁶⁻¹⁹

Exclusion criteria were the following:

- Acute ischemic mitral regurgitation;
- Ischemic isolated type I or type II dysfunction²⁰;
- Previous cardiac surgery or cardiac resynchronization therapy procedure;
- Other significant valve disease (aortic, pulmonary, tricuspid);
- Concomitant ventricular procedures;
- Patients unable to exercise and unwilling to cooperate;
- Severe chronic obstructive pulmonary disease;
- Persistent mitral regurgitation (defined as postoperative, residual vena contracta width >3 mm, at the echocardiographic examination, before discharge²¹;
- Patients with <1 year of follow up;
- New onset of wall motion abnormalities, suggestive of myocardial ischemia, ischemic echocardiogram changes, and angina, during ESE; and
- Atrial fibrillation.

Surgical indication was given during a multidisciplinary meeting. The choice between the 2 surgical techniques (ie, RMA or MVR) was left to

the surgeon. This surgical policy was systematically applied in our center, by 2 high-volume senior surgeons who had a special interest in mitral valve surgery. Given the absence of clear superiority of 1 of the 2 techniques, the decision of which to use was made in terms of risk/benefit ratio.

The 2 groups received the same preoperative, operative, and postoperative care. Six (2.8%) perioperative deaths occurred (deaths within 30 days or before discharge from the index hospitalization), with no difference between RMA and MVR. The final population of 121 patients (RMA = 62; MVR = 59) underwent a noninvasive, hemodynamic evaluation and a functional capacity assessment, using ESE and 6-MWT distance, respectively (Figure 1). The mean follow-up time (ie, time from surgery to the 2 assessments) was 41 ± 16.5 months (range, 12-65 months), without significant difference between the 2 groups (RMA: 43 ± 16 months; MVR: 38 ± 17 months, $P = .1$). Ethical approval was given by the local hospital committee, and informed consent was obtained from all patients.

Echocardiographic and Clinical Data

Coronary angiographic findings; preoperative, intraoperative, and postoperative clinical data; and Doppler echocardiographic findings were prospectively collected in our institutional, computerized database. For the eligible portion of the population, clinical information was obtained through an outpatient clinic, and was 90% complete. Postoperative cardiac events were defined as the occurrence of death or cardiac-related hospitalization, as recommended in the American College of Cardiology/American Heart Association guidelines.^{22,23} Recurrent mitral regurgitation was defined as a vena contracta width of >3 mm, at follow-up appointments, in patients who had either no or trivial mitral regurgitation at discharge.¹⁷

Surgery

Both procedures were performed by median sternotomy. The mitral valve was approached through a conventional left atriotomy. In all patients, visual inspection by the surgeon confirmed the preoperative inclusion criteria. In the RMA group, the ring sizer was selected by measuring the intercommissural distance of the mitral valve, and positioned to cover the surface of the stretched middle scallop of the anterior leaflet. A downsizing by 2 ring sizes was performed in all patients.²⁴ Most (71%) of the patients who underwent RMA received a Carpentier-Edwards Physio Annuloplasty Ring I; the remaining patients (29%) received a Carpentier-Edwards Classic Annuloplasty Ring (both from Edwards LifeSciences, Irvine, Calif).

In the group who underwent MVR, biologic or mechanical prostheses were inserted with systematic preservation of the subvalvular apparatus. All the patients underwent associated coronary bypass surgery, and every vessel that could be grafted was grafted. Complete revascularization was considered to have been done when ≥ 1 graft was placed distal to an approximately 50% diameter narrowing in each of the 3 major vascular systems, and when this stenosis intraoperatively corresponded to a vessel of ≥ 1.5 mm, as previously recommended.¹⁷ According to the given definition, complete revascularization was performed in all patients.

Transesophageal echocardiography was always performed after cardiopulmonary bypass surgery, to assess potential residual mitral regurgitation. A leaflet coaptation length of ≥ 5 mm (mean, 0.78 ± 0.1 mm); a mitral regurgitation grade ≤ 1 , and a systolic mitral valve area of >2 cm² were considered the criteria for successful repair.²⁵

Exercise Stress Echocardiography and Functional Capacity Assessment

The postoperative ESE protocol, and the echocardiographic measurement obtained at rest and during exercise, were performed as described elsewhere.¹¹ The mitral regurgitation severity was quantified using the

FIGURE 1. Flowchart describing the patient population. *ESE*, Exercise stress echocardiography; *MR*, mitral regurgitation.

vena contracta method, as specified in the current literature.¹⁵ A measure of distance from the 6-MWT was taken, according to American Thoracic Society guidelines, before surgery and after surgery, on the same day as the postoperative ESE exam.²⁶

Statistical Analysis

Quantitative variables are expressed as mean $\pm$ SD. The population was studied in 2 groups, according to surgical treatment (RMA: $n = 62$ [51%]; MVR: $n = 59$ [49%]). Differences between quantitative variables were tested by *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables are expressed as proportions and were compared by χ^2 analysis or Fisher exact test, as appropriate. Preoperative and postoperative variables of patients who underwent RMA or MVR were compared by 2-way ANOVA for repeated measures.

Multivariate linear regression analysis was performed to investigate independent predictors of postoperative 6-MWT distance. Special care was taken to avoid collinearity in the multivariate model. Only variables with a univariate $P < .1$ were included in the multivariate model.

Type of surgery treatment (RMA or MVR) was systematically included in all multivariate models as a dummy variable. To reduce the effect of selection bias and potential confounding in this observational study, we developed a propensity score analysis. The propensity for RMA was determined without regard to outcome, by use of nonparsimonious multiple logistic regression analysis. All the preoperative variables were included in the analysis. A propensity score, indicating the predicted probability of receiving RMA treatment, was calculated from the logistic equation for each patient. Finally, propensity score and months of follow up were included in the multivariate analysis. All statistical analysis was performed with SPSS 15.0 (SPSS Inc, Chicago, Ill).

RESULTS

Preoperative Data

The preoperative data of the 121 patients are shown in [Table 1](#). No difference was found between the 2 groups in age, gender distribution, body surface area, or extent of coronary disease. However, a significant difference was

found between the 2 groups in functional capacity, as expressed by 6-MWT distance (RMA: 251 ± 43 m vs MVR: 235 ± 34 m, $P = .03$; [Table 1](#)). Among the total population, history of advanced heart failure (New York Heart Association class III/IV) was present in 51 (42%) patients, and 17 (14%) patients had atrial fibrillation, without significant differences between the RMA and MVR groups. Left ventricular function was severely depressed in both groups (RMA: $37\% \pm 6.7\%$; MVR: $39\% \pm 7.5\%$, $P = .06$).

In the MVR group, preoperative mitral regurgitation was severe in 46 (32%) patients and moderate in 20 (14%) patients, whereas in the RMA group, mitral regurgitation was severe in 58 (41%) patients and moderate in 18 (13%). Vena contracta width did not differ significantly between the RMA and MVR groups (7.2 ± 0.7 mm vs 7 ± 0.7 mm, $P = .2$, respectively; [Table 1](#)). Among the eligible population ($n = 121$), 70 (58%) patients had experienced a myocardial infarction within the 3 months preceding surgery, without a significant difference between the RMA and MVR groups ([Table 1](#)).

Operative Data

The results showed no significant difference between the 2 groups in regard to operative data (ie, cardiopulmonary bypass time, aortic cross-clamp time, number of grafted vessels, number of arterial grafts, and type and number of conduits used). The RMA was performed using a Carpentier-Edwards Physio Ring I (Edwards LifeSciences) with a size of 26 mm, in 8 (13%) patients, a size of 28 mm in 36 (58%) patients, 30 mm in 17 (27%) patients, and 32 mm in 1 (2%) patient. A Carpentier- Edwards Classic

TABLE 1. Preoperative data

Variable	Total cohort (n = 121)	RMA group (n = 62)	MVR group (n = 59)	P value
Clinical				
Female gender	50 (42)	24 (38)	26 (44)	.6
Age (y)	65.2 ± 5	65 ± 4.6	65.5 ± 5.4	.6
BSA (m ²)	1.8 ± 0.11	1.77 ± 0.15	1.79 ± 0.05	.3
Diabetes	26 (22)	14 (22)	12 (20)	.6
Systemic hypertension	74 (61)	36 (58)	38 (64)	.5
Smoking history	76 (63)	42 (67)	34 (57)	.4
Dyslipidemia	78 (64)	41 (66)	37 (67)	.7
Cerebrovascular disease	7 (5)	2 (3)	5 (8)	.2
Recent MI	44 (36.4)	25 (40.3)	19 (32.2)	.4
Preoperative IABP	13 (10.7)	7 (5.8)	6 (5)	.8
Angina	49 (40.5)	23 (37)	26 (44)	.4
Functional				
6-MWT distance (m)	243 ± 40	251 ± 43	235 ± 34	.03
NYHA class III/IV	51 (42)	25 (39)	26 (46)	.2
Echocardiographic				
LVEF (%)	38 ± 7.2	37 ± 6.7	39 ± 7.5	.06
VC width (mm)	7 ± 0.7	7.2 ± 0.7	7 ± 0.7	.2
LA (mm)	50.9 ± 5.3	51.4 ± 4.9	50.4 ± 5.6	.3
Mitral annular diameter (mm)	43.1 ± 2.3	43.3 ± 2.36	42.9 ± 2.2	.48
Angiographic				
No. of diseased coronary vessels				.13
1	6 (4.9)	1 (0.8)	5 (4.1)	
2	29 (23.9)	13.2 (20)	16.7 (27)	
≥3	86 (71)	48.7 (77)	38.9 (64)	
Left main	17 (14)	8 (12.9)	9 (15.2)	.7
LAD territory	120 (99)	62 (100)	58 (98)	.9
Left circumflex territory	57 (47.1)	32 (26.4)	25 (20.7)	.3
RCA territory	67 (55.4)	35 (28.9)	32 (26.4)	.8

Values are n (%) or mean ± SD, unless otherwise indicated. *P* values refer to differences between the RMA and MVR groups. RMA, Restrictive mitral annuloplasty mitral; MVR, mitral valve replacement; BSA, body surface area; MI, myocardial infarction; IABP, intra-aortic balloon pump; 6-MWT, 6-minute walking test; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; VC vena contracta; LA, left atrium; LAD, left anterior descending; RCA, right coronary artery.

Annuloplasty Ring (Edwards LifeSciences), size 26 mm, was used in 5 (8%) patients; size 28 mm was used in 9 (15%) patients; and size 30 mm was used in 4 (6%) patients.

In the MVR group, 16 (27%) patients received a Carpentier-Edwards Perimount Pericardial bioprosthesis (Edwards LifeSciences) size 27 mm, 15 (25%) patients received size 29, and 1 (2%) patient received size 31. A mechanical St Jude Medical valve (St Jude Medical Inc, St Paul, Minn), size 27 mm, was used in 7 (12%) patients; a size 29 was used in 19 (32%) patients; and a Carbomedics (Sulzer Carbomedics, Inc, Austin, Tex [division of Sulzer Medical]), size 27 mm, was used in 1 (2%) patient. The extent of surgical revascularization was similar in the 2 groups (number of grafts: 2.5 ± 0.6 in the RMA group vs 2.7 ± 0.8 in the MVR group; *P* = .5).

Resting Preoperative and Follow-up Echocardiographic Data

At follow up, left ventricular diameters, indexed for body surface area, significantly decreased in both the RMA and MVR groups, without a significant difference between the

2 groups (*P* = .9 for left ventricular, indexed, end-diastolic diameter; *P* = .1 for left ventricular, indexed, end-systolic diameter). The left ventricular ejection fraction significantly improved in both groups (RMA from 37% ± 6.7% to 40% ± 4.3%; MVR: from 39% ± 7.5% to 42% ± 5.7%; *P* < .001), without a significant difference between the 2 groups (*P* = .9; Table 2). Effective cardiac output and cardiac index increased to a greater extent in the MVR group, compared with the RMA group (5.1 ± 1 vs 4.3 ± 0.8 L/minute for cardiac output, *P* = .007, respectively; and 2.8 ± 1 vs 2.4 ± 0.3 L/minute/m², for cardiac index, *P* = .005, respectively).

At follow up, vena contracta width decreased from 7.2 ± 0.7 to 3 ± 2.4 mm (*P* < .001; Table 2). In the RMA group, 25 (40%) patients experienced mitral regurgitation recurrence, which was severe for 9 (14%) of them. Systolic pulmonary arterial pressure significantly decreased within the 2 groups (RMA: from 40 ± 9 to 39 ± 7 mm Hg; MVR: from 38 ± 10 to 32 ± 6 mm Hg; *P* = .001; Table 3); however, the percentage of reduction of systolic pulmonary arterial pressure was higher in the MVR group (RMA: −2.5% ± 5% vs MVR: −16% ± 8%; *P* = .04; Table 2).

TABLE 2. Resting preoperative and follow-up echocardiographic data

Variables	Total (n = 121)	RMA (n = 62)		MVR (n = 59)		ANOVA <i>P</i> value	
	Preop.	Preop.	Follow up	Preop.	Follow up	Within	Between
LV geometry							
LVEF (%)	38 ± 7.2	37 ± 6.7	40 ± 4.3	39 ± 7.5	42 ± 5.7	.0001	.9
EDD (mm)	60 ± 4.9	61 ± 4.7	55 ± 5	60 ± 5	56 ± 4.4	<.001	.03
IEDD (mm/m ²)	36 ± 4.2	36 ± 4.7	34 ± 2.7	35 ± 3.4	33 ± 4.4	<.001	.9
ESD (mm)	47 ± 9.6	49 ± 11.6	44 ± 5.3	46 ± 6.9	42 ± 6	<.001	.6
IESD (mm/m ²)	28 ± 5.4	31 ± 5.1	28 ± 3.6	26 ± 4.7	25 ± 5.2	.001	.1
Mitral valve hemodynamics							
Peak gradient (mm Hg)	3.3 ± 0.8	3.3 ± 0.8	8.5 ± 2.9	3.4 ± 0.8	8.3 ± 4	<.001	.15
Mean gradient (mm Hg)	1.5 ± 0.2	1.6 ± 0.3	4.4 ± 1.4	1.6 ± 0.2	4.3 ± 1.8	<.001	.11
SPAP (mm Hg)	39 ± 9.6	40 ± 9	39 ± 7	38 ± 10	32 ± 6	.001	.02
VC width (mm)	7 ± 0.7	7.2 ± 0.7	3 ± 2.4*	7 ± 0.7†	—		
CO (L/min)	4.4 ± 0.5	4.3 ± 0.4	4.3 ± 0.8	4.5 ± 0.6	5.1 ± 1	.5	.007
CI (L/min/m ²)	2.5 ± 0.3	2.4 ± 0.2	2.4 ± 0.3	2.5 ± 0.3	2.8 ± 1	.5	.0005

Analysis of variance within patients (preoperative vs postoperative), and between the 2 groups (RMA vs MVR): **P* < .001 preoperative versus follow up; †*P* = .2 preoperative RMA versus preoperative MVR comparison. *RMA*, Restrictive mitral annuloplasty; *MVR*, mitral valve replacement; *ANOVA*, analysis of variance; *Preop.*, preoperative; *LV*, left ventricle; *LVEF*, left ventricle ejection fraction; *EDD*, end diastolic diameter; *IEDD*, indexed end diastolic diameter; *ESD*, end systolic diameter; *IESD*, indexed end systolic diameter; *SPAP*, systolic pulmonary arterial pressure; *VC*, vena contracta; *CO*, cardiac output; *CI*, cardiac index.

Resting and Exercise Follow-up Echocardiographic Data

The resting and exercise follow-up echocardiographic data are reported in Table 3. Resting left ventricular ejection fraction, indexed effective orifice area, and cardiac output were significantly higher in the MVR versus the RMA group. Mitral mean and peak gradients were not significantly different in the 2 groups. Systolic pulmonary arterial pressure was lower in the MVR versus the RMA group (Table 3). The percentages of age-predicted maximal heart rate, maximal workload, peak systolic blood pressure, and heart rate did not differ significantly between the RMA and MVR groups.

The exercise-induced increase in indexed effective orifice area was significantly higher in the MVR group, compared with the RMA group (RMA: from 1.1 ± 0.3 to 1.2 ± 0.2 cm²/m²; MVR: from 1.3 ± 0.2 to 1.5 ± 0.3 cm²/m²; *P* = .001). The mean mitral gradients significantly increased, from rest to exercise, to a greater extent in the RMA group (RMA: from 4.4 ± 1.4 to 11 ± 3.6 mm Hg; MVR: from 4.3 ± 1.8 to 9 ± 3.5 mm Hg; *P* = .006; Table 4). Exercise systolic pulmonary arterial pressure was significantly higher in the RMA group, compared with the MVR group (RMA: change from 39 ± 7 to 55 ± 10 vs MVR: change from 32 ± 6 to 41 ± 11 mm Hg; *P* = .001). The cardiac output significantly increased from

TABLE 3. Resting and exercise follow-up echocardiographic data

Mitral valve hemodynamics	Total (n = 121)	RMA (n = 62)	MVR (n = 59)	<i>P</i> value
Resting				
LVEF (%)	41 ± 5.2	40 ± 4.3	42 ± 5.7	.005
EOA (cm ²)	2 ± 0.5	1.8 ± 0.6	2.2 ± 0.4	.02
IEOA (cm ² /m ²)	1.2 ± 0.3	1.1 ± 0.3	1.3 ± 0.2	.001
MPG (mm Hg)	8.4 ± 3	8.5 ± 2.9	8.3 ± 4	.7
MMG (mm Hg)	4.3 ± 1.6	4.4 ± 1.4	4.3 ± 1.8	.7
SPAP (mm Hg)	35 ± 7.3	39 ± 7	32 ± 6	<.001
CO (L/min)	4.7 ± 1	4.3 ± 0.8	5.1 ± 1	<.001
CI (L/min)	2.7 ± 0.5	2.5 ± 0.4	2.9 ± 0.6	<.001
Exercise				
LVEF (%)	48 ± 6.6	46 ± 7.2	49 ± 5.6	.01
EOA (cm ²)	2.1 ± 0.5	1.9 ± 0.5	2.2 ± 0.4	<.001
IEOA (cm ² /m ²)	1.3 ± 0.3	1.2 ± 0.3	1.5 ± 0.3	<.001
MPG (mm Hg)	18 ± 8.1	21 ± 6.5	16 ± 8.8	.008
MMG (mm Hg)	10 ± 3.7	11 ± 3.6	9 ± 3.5	.006
SPAP (mm Hg)	48 ± 12	55 ± 10	41 ± 11	<.001
CO (L/min)	8.2 ± 1.5	7.5 ± 1.5	8.8 ± 1.4	<.001
CI (L/min)	4.6 ± 0.8	4.3 ± 0.8	4.9 ± 0.8	<.001

Values are mean ± SD. *RMA*, Restrictive mitral annuloplasty; *MVR*, mitral valve replacement; *LVEF*, left ventricle ejection fraction; *EOA*, effective orifice area; *IEOA*, indexed EOA; *MPG*, mitral peak gradient; *MMG*, mitral mean gradient; *SPAP*, systolic pulmonary arterial pressure; *CO*, cardiac output; *CI*, cardiac index.

TABLE 4. Univariate determinants of and relative changes in 6-minute walking test at follow up

Measure	6-MWT			
	β	SD	R ²	P value
Preop. 6-MWT	0.4	0.1	0.18	<.001
Exercise				
IEOA	0.29	0.12	0.079	.001
EF	0.4	0.7	0.15	<.001
SPAP	−0.22	0.4	0.04	.001
CO	0.24	3.2	0.05	<.001
CI	0.24	2	0.05	.01
Resting				
CI	0.23	9.9	0.04	.01
EF	0.15	1	0.02	.09
SPAP	−0.28	0.7	0.07	.002
Recurrent MR	−0.37	12.1	0.13	<.001

6-MWT, 6-minute walking test; SD, standard deviation; Preop., preoperative; IEOA, indexed effective orifice area; EF, ejection fraction; SPAP, systolic pulmonary arterial pressure; CO, cardiac output; CI, cardiac index; MR, mitral regurgitation.

rest to exercise to a greater extent in the MVR group ($P = .001$; Table 3).

Determinants of Functional Capacity

The results showed no significant difference between the groups in the time interval between surgery and the postoperative distance obtained on the 6-MWT. Figure 2, A shows the preoperative and postoperative distance, in the total population and in the 2 groups (RMA vs MVR). In the whole cohort, the distance did not statistically improve after surgery (from 243 ± 40 to 249 ± 58 m; $P = .20$). Comparing the 2 groups, 6-MWT distance significantly increased in the MVR group only (from 235 ± 34 to 272 ± 53 m; $P = .001$) whereas it decreased in the RMA group (from 251 ± 43 to 227 ± 54 m; $P = .001$).

$P = .001$; Figure 2, A). Figure 2, B shows 6-MWT time, stratified in the 2 groups.

Table 4 shows the univariate determinants of postoperative 6-MWT distance, at follow up (ie, the preoperative vs postoperative difference). The preoperative 6-MWT distance, recurrent mitral regurgitation, exercise indexed effective orifice area, exercise ejection fraction, exercise cardiac output, and resting and exercise systolic pulmonary arterial pressure were univariate determinants of distance on the 6-MWT, at follow up. Furthermore, all these variables, with the addition of resting ejection fraction, were significant univariate determinants of change in 6-MWT distance.

On multivariate analysis, preoperative 6-MWT distance ($P = .001$), age ($P = .04$), MVR ($P = .01$), exercise indexed effective orifice area ($P = .03$) and exercise ejection fraction ($P = .02$) resulted in an independent relationship with 6-MWT distance. At follow up, MVR ($P = .003$), exercise indexed effective orifice area ($P = .03$), exercise ejection fraction ($P = .01$), and exercise cardiac index ($P = .02$) were significant independent predictors of 6-MWT distance (Table 5, first model). When recurrent mitral regurgitation (vena contracta width >3 mm) was included as a covariate in a second multivariate model (Table 5, second model), all the aforementioned variables were confirmed as independent determinants of 6-MWT distance. In this second model, recurrent mitral regurgitation itself was not independently associated with 6-MWT distance, at follow up ($P = .23$ and .15).

Clinical Outcome

At 5-year follow up, survival was 83% in the RMA group and 88% in the MVR group ($P = .54$; Figure 3). In the

FIGURE 2. A, Preoperative and postoperative 6-MWT distance in the whole cohort, and by surgical treatment: RMA versus MVR. B, 6-MWT distance, stratified by time in the 2 groups. MVR, Mitral valve replacement; RMA, restrictive mitral annuloplasty.

TABLE 5. Multiple linear regression

Variables	6-MWT		
	β	SD	P value
First model			
Age	−0.241	0.71	.02
Gender	−0.035	7.65	.6
MVR	0.35	8.8	.001
Exercise IEOA, cm ² /m ²	0.226	13.01	.02
Exercise EF, %	0.33	0.59	.001
Preop. 6-MWT, m	0.62	0.11	.001
Second model			
Age	−0.236	0.7	.01
Gender	−0.032	7.6	.62
MVR	0.36	8.7	.001
Exercise IEOA	0.22	12.9	.02
Exercise EF	0.3	0.61	.001
Recurrent MR	−0.11	8.5	.1
Preop. 6-MWT	0.6	0.1	.001

6-MWT was adjusted for propensity score and time-interval follow-up. Second model was adjusted for vena contracta width >3 mm, at follow-up. 6-MWT, 6-minute walking test; SD, standard deviation; MVR, mitral valve replacement; IEOA, indexed effective orifice area; EF, ejection fraction; MR, mitral regurgitation; Preop., preoperative.

RMA group, 12 (70% ± 9.5%) patients experienced rehospitalization for heart failure, versus 6 (63% ± 7%) patients in the MVR group, without significant difference ($P = .31$) between the 2 groups.

DISCUSSION

The most important finding of this study is that, in patients with CIMR who underwent mitral valve surgery, the improvement in functional capacity at long-term follow up, as assessed using the 6-MWT, is mainly related to the type of treatment (MVR vs RMA) and to the mitral valve hemodynamic performance, as expressed by changes in indexed effective orifice area during exercise.

FIGURE 3. Kaplan-Meier curves, stratified by group (RMA vs MVR). MVR, Mitral valve replacement; RMA, restrictive mitral annuloplasty.

Hemodynamic Implications

The pathophysiologic mechanism underlying CIMR is related to the outward displacement of the posterior and anterior papillary muscles, owing to left ventricle remodeling, which causes annular dilatation, leaflet tethering, and mitral valve deformation. These factors lead progressively to a miscoaptation with a central or posterior regurgitation jet. The displacement of the papillary muscles further tethers the chordae, reducing the diastolic flexibility and the motion of the leaflets.^{27,28}

The rationale of RMA is to reduce the mitral annulus, by shortening the anteroposterior distance with a prosthetic ring, selected to be 2 sizes below the measured intertrigonal length.²⁴ In the annuloplasty, the insertion of a prosthetic ring fixes the posterior leaflet and markedly reduces its mobility, such that valve closure becomes essentially a single-leaflet process.²⁰ Meanwhile, the subvalvular apparatus remains untreated, worsening the tethering. This mechanism contributes to further restriction of the systolo-diastolic motion of the mitral valve and may explain the presence of some degree of functional mitral stenosis, which may worsen during exercise.¹⁰ Kubota and colleagues²⁹ reported a persistent subvalvular leaflet tethering, as a potential cause of postoperative functional mitral stenosis, associated with significant exercise-induced worsening of symptoms.

In our study, we found that during exercise, the increase in indexed effective orifice area was significantly higher in the MVR group, compared with the RMA group, leading to better hemodynamic performance. These findings are in line with previous studies that reported a better mitral valve opening reserve (ie, changes from rest to exercise) in the MVR group, compared with the RMA group.^{10,11,29}

The reason for the higher indexed effective orifice area increment in the MVR group, during exercise, may be related to the fact that this area of the prostheses depends on the transvalvular flow and, unlike the ring, is not under the influence of the subvalvular tethering. Conversely, in the annuloplasty group, the insertion of a prosthetic ring considerably reduced the diastolic expansion of the mitral annulus. Other studies have focused on the diastolic expansion of the mitral annulus as a key mechanism involved in the mitral valve orifice opening during diastole.³⁰

Magne and colleagues¹⁰ reported a higher stress peak gradient and systolic pulmonary arterial pressure, along with reduction of the indexed effective orifice area, in patients who had undergone RMA. These hemodynamic sequels were associated with worse functional capacity.¹⁰ In our study, we found that the type of treatment (ie, RMA), along with reduced indexed effective orifice area and limited increase in the cardiac index and left ventricular ejection fraction during exercise, were the most significant predictors of postoperative functional

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capacity. Other factors, such as right ventricular or pulmonary vascular function, that may contribute to exercise performance remain to be determined.

Clinical Implications

The Cardiothoracic Surgical Trials Network is conducting a multicenter randomized trial to evaluate the relative benefits and risks of RMA versus MVR, in patients with CIMR. The 1-year results showed no difference in left ventricular reverse remodeling and survival between the 2 treatment groups. Moreover, no significant difference has been found between the 2 in functional status or quality of life.⁹ This trial evaluated functional status, by using the Minnesota Living with Heart Failure Questionnaire. As reported in a previous study,³¹ the effectiveness of an intervention should be additionally evaluated by using the quality-of-life questionnaire, along with measures of physical functional capacity. For this purpose, the 6-MWT distance measure is reproducible and has been shown to be an adequate alternative to cardiopulmonary testing.^{12,13} In the group who underwent RMA, the presence of some degree of functional mitral stenosis, expressed as limited indexed effective orifice area during exercise, was associated with low cardiac output and cardiac index. All these hemodynamic findings are in line with other studies^{10,29} and may explain the negative impact of RMA on functional capacity, as expressed by a reduction in the 6-MWT distance.

To avoid functional mitral stenosis, with its resultant negative impact on hemodynamic performance and functional capacity, the best approach is to perform less-restrictive RMA, to limit as much as possible the reduction in posterior leaflet mobility, and thereby limit subvalvular tethering. However, the strategy of using less restriction would probably lead to a higher rate of persistent and/or recurrent mitral regurgitation. The progression of ventricular remodeling further worsens the leaflet tethering, and these 2 main components, along with reduced diastolic motion of the posterior annulus, may contribute to the poor durability after annuloplasty. In light of these factors, the newer rings, such as the saddle-shaped ring, seem to offer promise in reducing the risk of both mitral regurgitation recurrence and functional mitral stenosis.³²

With a goal of treating the causal mechanism of CIMR, several clinical and experimental procedures have been evaluated for their ability to improve left ventricular and subvalvular geometry.³³⁻³⁵ The findings of this and other studies⁸ underline the importance of tailoring the surgical procedure according to the baseline characteristics of the patient.

Limitations

The main limitation of the present study is its retrospective design, which creates potential selection

bias. A potential survivor bias may influence the comparison between groups regarding the 6-MWT. Nevertheless, the number of deaths and rate of death were similar between the 2 groups, limiting this bias. In our series, the choice of type of surgery (ie, RMA vs MVR) was made by the surgeon. However, the vast majority of patients underwent surgery, with 1 of only 2 senior surgeons, who both had recognized expertise in mitral valve surgery, and produce similar surgical outcomes.

We used a distance measure from the 6-MWT, rather than results of a cardiopulmonary exercise test. However, this latter test requires specialized equipment and trained personnel, which may limit its use. Moreover, 6-MWT distance is widely used in assessment of patients with heart failure of any etiology and mostly in patients with moderate ventricular impairment, as encountered in our study population.

In addition, although this study is based on longitudinal data, we reported a measurement from only a single 6-MWT and ESE, rather than repeated measures over time. Therefore, we do not know if these outcomes might change over time, for either group. Three-dimensional transesophageal measurements of the mitral annulus were not available.¹⁵

We have very limited information regarding preoperative myocardial viability in the 2 groups. Thus, a potential lack of left ventricular remodeling in patients with annuloplasty might be the result of irreversible ischemic myocardial damage, which could be detected by viability testing. Postoperative evaluation of coronary status was not conducted. It would be interesting to know if progression of coronary disease contributed to the different outcomes between the 2 treatment groups.

We acknowledge the lack of more echocardiographic data, such as tenting height, and particularly the posterior leaflet angle; such data would have been helpful. The annuloplasty ring was undersized by 2 sizes, in all patients, regardless of the symmetric or asymmetric pattern of ischemic mitral regurgitation, and this factor could have influenced the results. In this regard, our findings should be carefully evaluated in patients receiving other types of rings, such as those specifically designed to correct CIMR. Finally, we did not investigate independent predictors of clinical outcomes, because of the relatively small number of cardiovascular events and lack of statistical power.

CONCLUSIONS

In patients with CIMR, MVR with total preservation of the subvalvular apparatus seems to be associated with better postoperative-exercise hemodynamic performance and long-term functional capacity, compared with RMA. Procedures aiming to restore ventricular geometry or targeting subvalvular mechanisms seem to be promising options, but establishing their usefulness requires further

scientific evidence. Pending the 24-month results from the Cardiothoracic Surgical Trials Network, MVR with chordal sparing may be a reliable option for these challenging patients.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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