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CLINICAL RESEARCH
Cardiovascular surgery

Five-year echocardiographic results of combined undersized mitral ring annuloplasty and coronary artery bypass grafting for chronic ischaemic mitral regurgitation

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Aims We present 5-year echocardiographic results of combined undersizing mitral ring annuloplasty (UMRA) and coronary artery bypass grafting (CABG) in chronic ischaemic mitral regurgitation (CIMR).

Methods and results Two hundred and fifty-one patients (aged 68.4 ± 8.1, 62.5% male) undergoing combined CABG and UMRA in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between September 2001 and March 2007 were prospectively enrolled in the study. Median follow up was 32.9 months [interquartile range (IQR) 17.5–51.6]. Fourteen patients with significant residual mitral regurgitation (MR) needing immediate intraoperative revision ($n = 3$) or at discharge ($n = 11$) were excluded from the study. Serial echocardiograms were performed in 220 survivors at baseline, discharge, and annually thereafter. Additionally, 17 patients died (2 early and 15 late deaths) and were also excluded from the study. MR remained stable at 1 year and re-increased at 3 years ($P < 0.001$) and 5 years ($P < 0.001$). Five-year actuarial survival was 83.2 ± 4.4. Five-year freedom from re-operation for failed repair was 78.2 ± 4.9%. Mean systolic and diastolic diameters decreased significantly at discharge ($P = 0.001$ and $P = 0.01$, respectively) and at early follow up ($P = 0.004$ and $P = 0.02$) but raised at 3 years ($P < 0.001$) and 5 years ($P < 0.001$). Systolic and diastolic sphericity indexes improved at discharge ($P < 0.001$) remained stable at 1 year but they re-increased at 3-year control ($P = 0.006$ and $P = 0.03$, respectively) with a late raise exceeding the pre-operative value ($P < 0.001$). Left ventricular reverse remodelling was observed in 44.2% of the study population with 10.3% of patients showing further left ventricular dilatation. At multivariable model, end-systolic volume ≥145 mL, systolic sphericity index ≥0.7, myocardial performance index ≥0.9, and wall motion score index ≥1.5 were predictors of recurrent MR.

Conclusion Our findings emphasize the need for improved repair technique and better patient selection to identify patients with anticipated repair failure who could benefit more from valve replacement or other procedure directly addressing ventricular tethering.

Keywords Mitral valve • Mitral regurgitation • Mitral valve repair

Introduction

Despite of improvements in mitral reparative techniques in the recent years,[1] chronic ischaemic mitral regurgitation (CIMR) still remains a challenging surgical problem. Combined coronary artery bypass grafting (CABG) and annular reduction with an annuloplasty ring (undersized mitral ring annuloplasty, UMRA) is the most common surgical technique employed to relieve ischaemic

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regurgitation.[2] Nonetheless, conflicting data are reported in the literature about long-term effectiveness of this approach.[3–7]

In the present study, we present 5-year echocardiographic results after combined UMRA and CABG in terms of recurrence of mitral regurgitation (MR), global and local LV remodelling, and left ventricular reverse remodelling (LVRR). We also explore potential useful predictors of recurrence of MR following combined undersized annuloplasty and coronary artery bypass.

Methods

Patients population

CIMR was defined as the combination of mild-to-severe MR with (i) prior myocardial infarction (MI) >16 days; (ii) 75% or greater stenosis of at least one coronary vessel; (iii) a corresponding regional wall motion abnormality; (iv) type IIIb leaflet dysfunction following Carpentier's classification[8] with or without annular dilatation.

Exclusion criteria were: (i) degenerative or other non-ischaemic aetiology; (ii) ischaemic isolated type I or type II dysfunction;[8] (iii) additional mitral valve repair procedures; (iv) other valvular or congenital heart diseases; (v) previous cardiac surgery/percutaneous transluminal coronary angioplasty; (vi) atrial fibrillation or sinus rhythm with heart rate at rest >100 b.p.m.

Two hundred and fifty-one patients undergoing combined CABG and UMRA in our Institution (Cardiac Surgery, Careggi Hospital, Florence, Italy) between September 2001 and March 2007 were prospectively enrolled in the study (*Table 1*). Clinical follow-up information was obtained from all survivors through outpatient visits and phone calls and was 100% complete. Median follow up was 32.9 months [interquartile range (IQR) 17.5–51.6].

Table 1 Peri-operative data (n = 251)

Age (year)	68.4 ± 8.1
Gender, M/F	155/93 (62.5/37.5)
NYHA class	3.2 ± 0.6
CCS angina class	3.09 ± 0.4
Euroscore	
Additive	8.0 ± 4.3
Logistic	13.6 ± 6.1
Hypertension	92 (36.6)
Diabetes	71 (28.62)
COPD	32 (12.7)
Chronic renal disease	26 (10.3)
Cerebral vascular disease	15 (6.0)
Peripheral vascular disease	11 (4.3)
Familiar history	101 (40.2)
Myocardial infarction	
>3 months	197 (78.4)
≤3 months	54 (21.6)
Inferior/posterior	122 (48.6)
Anterior/septal	22 (8.8)
Lateral	49 (19.5)
Combined	58 (23.1)
Diseased coronary vessels	2.4 ± 0.5
1	15 (6.0)
2	107 (42.6)
≥3	129 (51.4)
Left main	38 (15.1)
Medications	197 (78.4)
Angiotensin-converting enzyme inhibitors	132 (52.6)
β-adrenergic blockers	109 (43.4)
Long-acting nitrates	185 (73.7)
Diuretics	50 (19.9)
Digitalis	33 (13.1)
Calcium antagonists	
Pre-operative IABP	11 (4.3)
Surgery	
Cardioplegia	218 (86.8)
Antegrade	33 (13.2)
Antegrade and retrograde	
CPB time (min)	123 ± 31
CCL time (min)	92 ± 18
Surgical approach	
Left atriotomy	207 (82.4)
Transseptal	25 (10.0)
Transseptal extended to LA roof	19 (7.6)
Ring	
Carpentier classic[a]	133 (52.9)
Physio[a]	118 (47.1)
Ring size (mm)	27.4 ± 1.5
24 mm	10 (4.1)
26 mm	92 (36.6)
28 mm	112 (44.6)
30 mm	
CABG	37 (14. 7)
Anastomoses/patient	2.2 ± 1.1
Arterial graft/patient	1.07 ± 0.1

Continuous variables are presented as mean ± standard deviation; discrete variables are presented as percentage. Abbreviations: M/F, male/female; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; IABP, inta-aortic balloon pump; CPB, cardiopulmonary bypass; CCL, (aortic) cross-clamp; MR, mitral regurgitation; CABG, coronary artery bypass grafting.
[a]Edwards LifeSciences, Irvine, CA, USA.

Following the World Medical Association guidelines concerning ethical principles for medical research involving human subjects,[9] the study was approved by Institutional Ethics Board. Furthermore, all patients gave their informed consent.

Surgery

All patients underwent associated CABG. For the purpose of this study, complete revascularization was accomplished when, at least, one graft was placed distal to an approximately 50% diameter narrowing in each of the three major vascular system in which arterial narrowing of this severity was noted in a vessel≥1.5 mm of diameter. It was not considered necessary to bypass all obstructed diagonal branches of the anterior descending or marginal branches of the circumflex coronary arteries for a classification of complete revascularization. Following this definition, 100% patients underwent complete revascularization.

The ring size was determined by standard measurements of the inter-trigonal distance and anterior leaflet height. A downsizing by two ring sizes was performed in all patients. After cardiopulmonary bypass (CPB), a transesophageal echocardiography (TEE) was performed to assess residual MR: leaflet co-aptation $\geq$0.5 cm, MR$\leq$1, and systolic MV area $>$2 cm^2 was assessed as successful repair. Three patients needed immediate intraoperative revision for failed repair: all underwent mitral valve replacement and were excluded from the study.

Echocardiographic measurements and calculations

The clinical echocardiographic evaluation was as follows. A transthoracic echocardiogram (TTE) and a TEE were performed within 5 days before surgery and serial TTE were performed at discharge and annually thereafter. Eleven patients (4.4%) with residual MR defined as the insufficiency $\geq$2+ following valve repair documented at discharge were excluded from the study. Five-year echocardiograms were available from 61 patients (27.7%). This patient dropout was independent of the disease status and totally due to the different number of patients reaching different study intervals [1 year, 187 patients (85%); 3 year, 122 (55.4%)]. Echocardiographic studies were carried out on Acuson Sequoia imaging device equipped with a 3.5 MHz ultrasound transducer (Acuson Corporation, Mountain View, CA, USA). Standard parasternal and apical views (long-axis, short-axis, 2-4-5-chamber views) were employed. The reliability of echocardiographic measurements was assessed by calculating between-observer (I.C. and C.R.) interval of agreements of main direct measures used in this study in a different group of 20 subjects (10 MR).[10]

Mitral regurgitation

The following quantitative measurements were simultaneously employed to grade the severity of MR and final results were averages of measured values:[11–13](i) quantitative Doppler and (ii) proximal isovelocity surface area (PISA). For each measurement, minimum of three cardiac cycles were averaged. The respective thresholds for mild, moderate, and severe MR were $<$30, 30–59, and$\geq$60 mL/beat for regurgitant volume (RV), $<$30, 30–49, and $\geq$50% for regurgitant fraction (RF), $<$20, 20–39, and$\geq$40 mm^2 for effective regurgitant orifice (ERO), respectively. In patients with no or trivial MR by colour Doppler, RV, and RF were used as calculated, and ERO was assumed as null.

The tenting area (TA) was measured by the area enclosed between the annular plane and mitral leaflets from the parasternal long-axis view at mid-systole. The distance between leaflet co-aptation and the mitral annulus plane at early and end systole measured displacement of mitral co-aptation toward the LV apex.[14,15] Mitral annular areas were obtained from mitral annular dimensions in apical long-axis, four-chamber, and two-chamber views, using an ellipsoid assumption.[16]

Recurrent MR was the insufficiency $\geq$2+ at follow-up appointments in patients with no/trivial MR at discharge.

Global left ventricular remodelling

LV volumes and left ventricular ejection fraction (LVEF) were assessed by the bi-apical Simpson disk method.[17] According to Stellbrink *et al.*, [18] a decrease in LV end systolic volume $>$15% from baseline value was considered LVRR. The myocardial performance index (MPI) was measured using the method described by Tei *et al.*[19] Sphericity indexes were obtained at end diastole and end systole (SI_D and SI_S, respectively) as the volume of the left ventricle divided by the volume of a sphere with a diameter equal to the longest axis of the left ventricle measured in the apical view.[20] The wall motion score index (WMSI) was calculated according to a 17-segment model.[21]

Local left ventricular remodelling

The displacement of papillary muscles (PMs) was quantified as distances from well-defined anatomic landmarks at early and end systole.[14] Lateral and posterior displacements of anterior papillary muscles (APMs) and posterior papillary muscles (PPMs) were measured as distances from these fixed references. Separation between PMs was directly measured (from body to body of PMs). In the long-axis view, the apical displacement of the PPM was measured as the distance between the PM head and the fixed inter-valvular fibrosa (annular-papillary distance). The WMSI of the basal and mid-posterior and inferior segments for the PPM and of basal and mid-lateral and anterior segments for the APM were calculated.[22]

Statistical analysis

The sample size was determined by GraphPad StatMate release 2.00 (GraphPad Prism Software, Inc., San Diego, CA, USA). On the basis of preliminary data obtained by echocardiography and was determined on the basis of the following assumptions: Type I error of 0.05 (two-sided), power of 80%, difference in end systolic volume between patients with or without recurrent MR of 0.78, standard deviation of 2.4. The calculated study population was 300. However, 256 patients were recruited to allow for possible analytic problems while processing the or other eventualities potentially leading to patient attrition. Continuous variables are presented as mean and standard deviation (SD), categorical variables as *n/N* (%), odds ratios as OR, and pertinent 95% confidence intervals as CI. The bivariate association between the independent variables and recurrent MR was assessed by the Student's *t*-test, Mann–Whitney U test, χ^2 test, and Fisher exact test where appropriate.

Echocardiographic variables over time were analysed by means of ANOVA repeated measures followed by Tukey *post hoc* test and Friedman test, where appropriate to detect differences at different study points (discharge vs. baseline; 1 year vs. discharge; 3 years vs.1 year, and 5 years vs. 3 years).

Multivariable logistic regression analysis by means of a backward stepwise algorithm (cut-off for entry 0.05, for removal 0.10) was performed to select independent predictors of recurrent regurgitation. Model assumptions (linearity and additivity assumptions) were checked by piecewise cubic polynomials (spiline functions) and pooled interaction test,[23] respectively, and found to be satisfied. Goodness of fit of the final logistic regression models was assessed with the Hosmer–Lemeshow statistic[24] and predictive accuracy was assessed by the concordance (c) index.[23] Internal validation of predictors generated by multivariable logistic regression was performed by means of bootstrapping techniques, with 1000 cycles and generation of OR and bias corrected 95% CI.[23]

Optimal cut-off values were determined as the rounding cut-off that gives the maximum sum of sensitivity and specificity. This value should be the shoulder at the top left of the receiver operating characteristic (ROC) curve. Bootstrapping techniques were employed to validate the results. Cumulative probability for death and re-operation were estimated by use of the Kaplan–Meier method.

SPSS 12.0 (SPSS, Chicago, IL, USA) and Stats Direct 2.5.7 (StatsDirect, Sale, UK) were used for these calculations. Significance for hypothesis testing was set at the 0.05 two-tailed level.

Results

Overall survival

Early (30-day) mortality was 0.8% ($n = 2$, respiratory failure and low-output syndrome). During the follow-up 15 patients died: six of cardiac causes [heart failure ($n = 3$; 36, 45, and 54 months), myocardial infarction ($n = 2$; 31 and 42 months), and arrhythmia ($n = 1$; 59 months)], eight of non-cardiac causes [multi-organ failure ($n = 1$; 6 months), respiratory failure ($n = 1$; 14 months), infection ($n = 2$; 3 and 8 months), stroke ($n = 2$; 12 and 43 months), and malignancy ($n = 2$; 55 and 59 months)] and 1 of sudden, unexplained death (22 months). Five-year actuarial survival was 83.2 ± 4.4 (*Figure 1*).

Residual and recurrent mitral regurgitation

Among 220 patients surviving CABG and reductive annuloplasty (*Figure 2*), mean MR remained stable at 1 year and re-increased at 3-year ($P < 0.001$) and 5-year studies ($P < 0.001$, *Table 2*). At 5-year echocardiography, 17 patients (27.8%) had no/trivial recurrent MR, 17 (27.8%) had MR 2+, 19 (31.1%) 3+, and 8 (13.1%) 4+(*Figure 3*). Seventeen patients underwent re-operation for failed repair due to recurrent MR: four (3.7%) had a re-MV repair and 13 (12.1%) underwent mitral valve replacement. Freedom from re-operation for failed repair was 78.2 ± 4.9% (*Figure 4*).

Global left ventricular remodelling and left ventricular reverse remodelling

Ventricular diameters and left atrial dimensions reduced significantly at discharge ($P < 0.001$, $P = 0.005$, $P = 0.002$, respectively), showing no further significant change at subsequent controls (*Table 3*). Mean ESV and EDV decreased significantly at discharge ($P = 0.001$ and $P = 0.01$, respectively) and at early follow up ($P = 0.004$ and $P = 0.02$), but re-increased at 3-year ($P < 0.001$) and 5-year ($P < 0.001$) studies. Furthermore, ejection fraction and MPI did not show significant changes over time. Systolic and diastolic sphericity indexes improved at discharge ($P < 0.001$), remained stable at 1-year (P = ns) but they increased at 3-year control ($P = 0.006$ and $P = 0.03$ for SI_S and SI_D, respectively) with a late increase exceeding the pre-operative value ($P < 0.001$). Finally, WMSI reduced significantly at discharge, remained constant at 1 year, but re-increased at 3-year ($P = 0.02$) and 5-year ($P < 0.001$) echocardiograms. Sixty percent of patients ($n = 132$) showed reverse remodelling at discharge and percent of patients showing LVRR increased significantly at 1-year ($P < 0.001$), but it reduced at 3-year ($P < 0.001$) and 5-year ($P = 0.01$) studies (*Figure 5*).

Local left ventricular remodelling

For local remodelling (*Table 4*), indexes of posterior and lateral displacement of both PMs, PM separation, PPM fibrosa, and $WMSI_s$ were reduced significantly at discharge and remained constant at 1 year; nevertheless, PPM posterior (3 years, $P = 0.01$; 5 years, $P = 0.02$), PPM lateral (3 years, $P = 0.008$; 5 years, $P = 0.02$), PMs separation (3 years, $P < 0.001$; 5 years, $P = 0.02$) and PPM_s fibrosa ($P < 0.001$) re-increased significantly at subsequent

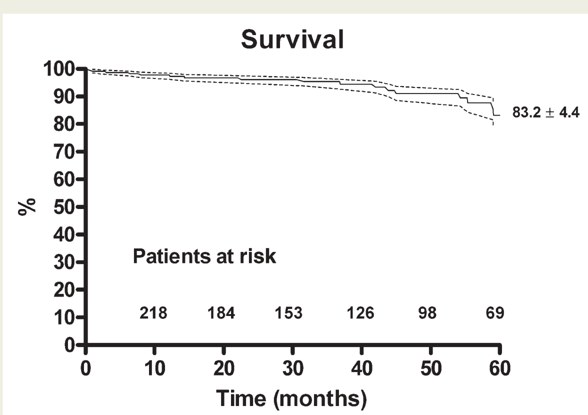

Figure 1 Five-year survival and 95% confidence interval (dotted lines) following undersized mitral ring annuloplasty and coronary artery bypass grafting in patients with ischaemic mitral regurgitation

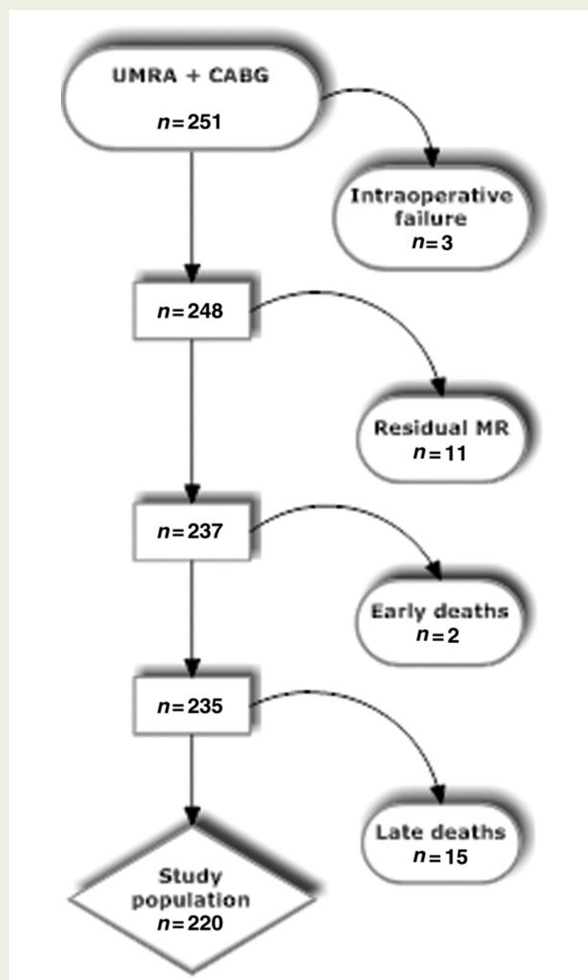

Figure 2 Patients selection. Abbreviations: UMRA, undersized mitral ring annuloplasty; CABG, coronary artery bypass grafting; MR, mitral regurgitation. See text for definitions

Table 2 Mitral regurgitation

	Baseline, $n = 220$	Discharge, $n = 220$	1 year, $n = 187$	3 years, $n = 122$	5 years, $n = 61$	*P
MR	3.1 ± 0.6	0.3 ± 0.5*	0.3 ± 0.6	$1.2 \pm 0.7^{\dagger}$	$2.1 \pm 1.2^{\ddagger}$	0.001
Direction of regurgitant jet						
Central	70 (31.8)	–	–	–	–	
Anterior	28 (12.7)	–	–	–	–	
Posterior	54 (24.6)	–	–	–	–	
Complex	68 (30.9)	–	–	–	–	
Carpentier's classification						
Type IIIb	134 (60.9)	–	–	–	–	
Type IIIb+annular dilatation	86 (39.1)	–	–	–	–	
Quantitative data						
TA	3.4 ± 1.1	1.9 ± 0.5*	1.9 ± 0.5	$2.1 \pm 0.6^{\dagger}$	$2.4 \pm 0.7^{\ddagger}$	<0.001
ERO	36 ± 11	–	–	–	$19 \pm 11^{\ddagger}$	–
RF	45 ± 10	–	–	–	$26 \pm 14^{\ddagger}$	–
RV	56 ± 13	–	–	–	$29 \pm 16^{\ddagger}$	–
CH	1.2 ± 0.3	$0.8 \pm 0.2^{\ddagger}$	0.8 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	0.02
MA_s	4.1 ± 1.2	2.6 ± 0.7*	2.6 ± 0.4	2.6 ± 0.7	2.6 ± 0.7	0.001
MA_d	5.0 ± 1.1	3.3 ± 0.5*	3.4 ± 0.6	3.4 ± 0.9	3.4 ± 0.9	<0.001
MΔp	–	2.3 ± 0.5	2.4 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	0.2

Continuous variables are presented as mean ± standard deviation. Discrete data are presented as n (%). P = ANOVA over time significance. MR, mitral regurgitation; TA, tenting area (cm^2); ERO, effective regurgitant orifice (mm^2); RF, regurgitant fraction (%); RV, regurgitant volume (mL); CH, co-aptation height (cm); MAs, (systolic) mitral annular area (cm^2); MA_d, (diastolic) mitral annular area (cm^2); MΔ*P*, *Trans* mitral diastolic gradient (mmHg).
*Significance vs. pre-operative (see text).
†One year (see text).
‡Three years (see text).

controls. In contrast, lateral and posterior displacements of the APM as well as WMSIs did not show further significant changes.

Predictors of recurrent mitral regurgitation

The unadjusted relationship between recurrent MR and independent variables are shown in *Table 5*. Multivariable logistic regression analysis identified systolic sphericity index (OR = 4.97, 95% CI = 2.11–6.40, $P < 0.001$), myocardial performance index (OR = 4.66, 95% CI=2.01–5.43, $P < 0.001$), end systolic volume (OR=2.59, 95% CI = 1.19–3.77, $P = 0.003$), and wall motion score index (OR = 1.99, 95% CI = 0.88–2.37, $P = 0.04$) as independent predictors of the occurrence of recurrent MR internal validation of such multivariable analysis by means of bootsrapping, including the same variables of standard logistic regression model,

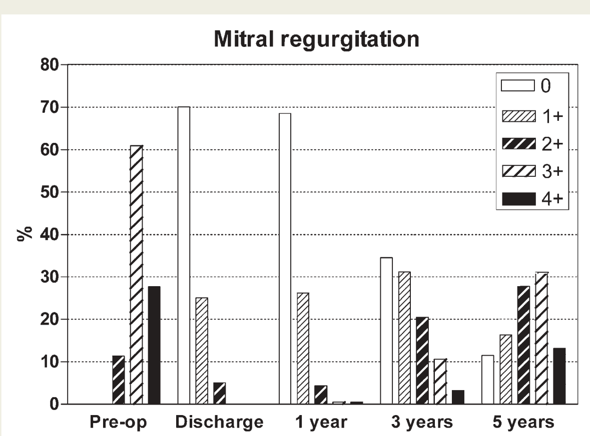

Figure 3 Mitral regurgitation (%) at different echocardiographic controls ($P < 001$)

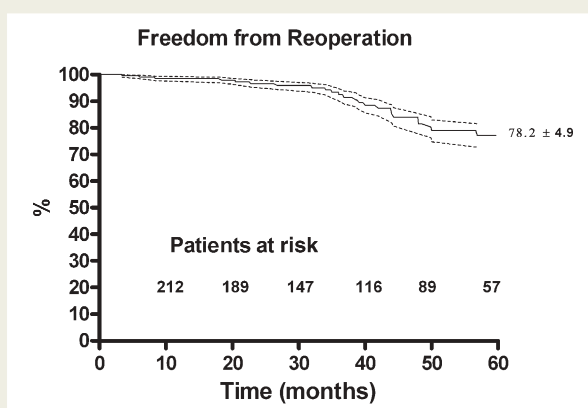

Figure 4 Five-year freedom from re-operation for recurrent ischaemic mitral regurgitation (dotted lines, 95% confidence interval)

Table 3 Global left ventricular remodelling

	Baseline	Discharge	1 year	3 years	5 years	P
EDD	62 ± 7	54 ± 7*	55 ± 7	53 ± 7	54 ± 7	0.03
ESD	52 ± 8	44 ± 6*	43 ± 6	42 ± 6	43 ± 6	0.04
LA	50 ± 7	45 ± 3*	46 ± 3	46 ± 3	46 ± 4	0.053
ESV	150 ± 24	114 ± 15*	108 ± 16†	121 ± 11‡	136 ± 11§	<0.001
EDV	195 ± 35	164 ± 26*	156 ± 19†	171 ± 23‡	191 ± 23§	0.02
LVEF	30 ± 12	31 ± 10	30 ± 10	30 ± 11	29 ± 12	0.38
MPI	0.79 ± 0.2	0.76 ± 0.1	0.75 ± 0.1	0.75 ± 0.1	0.76 ± 0.1	0.2
SI_S	0.65 ± 0.2	0.50 ± 0.1*	0.50 ± 0.1	0.58 ± 0.1‡	0.66 ± 0.2§	0.03
SI_D	0.72 ± 0.1	0.62 ± 0.1*	0.60 ± 0.1	0.66 ± 0.1‡	0.74 ± 0.1§	0.01
WMSI	1.4 ± 0.7	1.2 ± 0.3*	1.1 ± 0.2	1.3 ± 0.4‡	1.5 ± 0.5§	0.006

Continuous variables are presented as mean ± standard deviation. P = ANOVA over time significance. EDD, (left ventricular) end diastolic diameter (mm); ESD, (left ventricular) end systolic diameter (mm); LA, left atrium (mm); ESV, (left ventricular) end systolic volume (mL); EDV, (left ventricular) end diastolic volume (mL); LVEF, Left ventricular ejection fraction (%); MPI, myocardial performance index; SI_S, systolic sphericity index; SI_D, diastolic sphericity index; WMSI, wall motion score index.
*Significance vs. pre-operative (see text).
†Discharge (see text).
‡One year (see text).
§Three years (see text).

further confirmed the significant predictive of recurrent MR (bootstrap OR = 2.3, 95% bias-corrected 95% CI = 1.1–5.2). Finally, logistic regression model was reliable (Hosmer–Lemeshow test, $P = 0.7$) and accurate (c-index = 0.81).

ROC analysis showed that SI_S had 100% of sensitivity and specificity with an optimal cut-off ≥0.7 (95% CI by bootstrapping 0.58–0.81) (area under curve 1; 95% CI 0.70–1; $P < 0.001$).

MPI with a cut-off ≥0.9 (95% CI by bootstrapping 0.75–0.96) had 85% of sensitivity and 84% of specificity (area under curve 0.94; 95% CI 0.67–1; $P < 0.001$). In addition, ESV ≥145 mL (95% CI by bootstrapping 134–155) had 90% of sensitivity and specificity (area under curve 0.87; 95% CI 0.80–0.94; $P < 0.001$). Finally, WMSI ≥1.5 (95% CI by bootstrapping 1.35–1.62) had 80% of sensitivity and 82% of specificity (area under curve 0.81; 95% CI 0.77–0.91; $P = 0.002$).

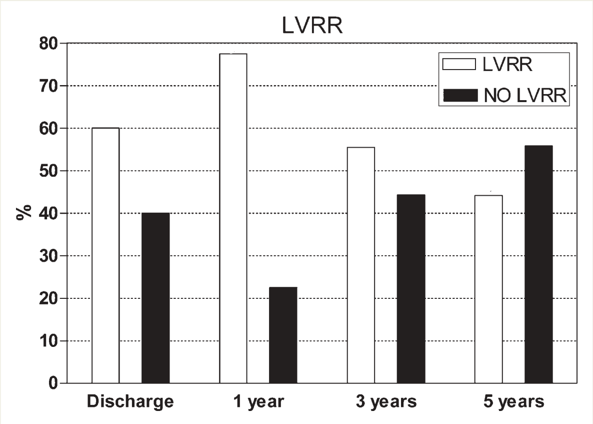

Figure 5 Left ventricular reverse remodelling ($P = 0.02$)

Discussion

An established therapeutic approach to relieve CIMR, in association with CABG, is an undersized mitral ring annuloplasty (UMRA)[2] which, by reducing the septal–lateral dimensions and the valve area, brings both mitral leaflets into apposition. Nonetheless, after encouraging initial results,[25] different studies have revealed a significant proportion of patients developing recurrent MR during follow-up[4,7,26] which has been mainly related to continued LV remodelling and persistent leaflet tethering.[5,27] We reported our experience with this technique. Patients were followed up by serial TTE over a 5-year period and recurrence of MR, local, and global LV remodelling, and LV reverse remodelling were explored. We also identified potential useful predictors of MR-recurrence following combined UMRA and CABG.

Because of unavailable complete echocardiographic data, 15 patients who died late after surgery were excluded from the study.

Recurrence of mitral regurgitation

In our report, recurrent MR significantly increased at 3-year and 5-year controls with and 27.8% of patients showing mild, 31.1%moderate, and 13.1% severe MR at latest follow-up. Five-year freedom from re-operation for failed repair was 78.2 ± 4.9%. Hung *et al.*[5] showed 72% of patients with moderate/severe MR at late control (47 ± 27 months) after ring annuloplasty and CABG. Accordingly, Tahta *et al.*[26] in a large single-centre surgical series reported a 29% incidence of MR ≥2 over a 3-year follow-up period. However, in these studies, annuloplasty had not been routinely performed in a restrictive fashion. In contrast with these results, Braun and coworkers[4] reported that, in 87 patients undergoing restrictive ring annuloplasty (2 ring sizes, median ring size 26), no patient showing MR ≥3 and 2 with MR graded 2+ at 18-month follow-up. In addition, Geidel *et al.*[28] reported that 15 of 29 patients having no MR (52%), nine patients with

Table 4 Local left ventricular remodelling

	Baseline	Discharge	1 year	3 years	5 years	*P*
PPM posterior D	2.6 ± 0.6	2.2 ± 0.5*	2.1 ± 0.3	2.3 ± 0.3†	2.5 ± 0.6‡	0.02
APM posterior D	2.9 ± 0.5	2.5 ± 0.2*	2.4 ± 0.3	2.4 ± 0.3	2.4 ± 0.3	<0.001
PPM lateral D	2.0 ± 0.4	1.6 ± 0.3*	1.6 ± 0.3	1.8 ± 0.3†	2.1 ± 0.3‡	0.01
APM lateral D	1.3 ± 0.3	1.0 ± 0.2*	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.008
PM_s separation	3.6 ± 0.5	3.2 ± 0.2*	3.0 ± 0.2	3.3 ± 0.2†	3.5 ± 0.4‡	<0.001
PPM-fibrosa D	6.7 ± 0.6	6.0 ± 0.4*	6.0 ± 0.4	6.4 ± 0.4†	6.6 ± 0.5‡	0.02
PPM WMSI	2.2 ± 0.2	2.0 ± 0.2*	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	0.03
APM WMSI	1.3 ± 0.4	1.0 ± 0.1*	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.003

Continuous variables are presented as mean ± standard deviation. *P* = ANOVA over time significance. D, distance (cm); PPM, posterior papillary muscle; APM, anterior papillary muscle; PMs, papillary muscles; WMSI, wall motion score index.
*Significance vs. pre-operative (see text).
†One year (see text).
‡Three years (see text).

MR1+ (31%), and five patients with MR2+ (17%), 13 ± 7 months after mitral annuloplasty and CABG. Of interest, they performed mitral downsizing in a 'dynamic fashion' dependent on LV function (2, 3, or4 ring sizes for LVEF>30, 20–30%,<20%, respectively).

Left ventricular remodelling

In our experience, we observed a significant global remodelling late after reductive annuloplasty: LV volumes increased significantly and WMSI exceeded its pre-operative value. Furthermore, LV became more spherical with sphericity indexes exceeding their baseline values at 5-year echocardiography. Regarding local remodelling, we observed a late 'asymmetric' lateral and posterior displacement of PPM with APM displacement which remained constant over time. Of interest, WMSI of the segments underlying both PMs, after a transient reduction, were relatively stable and these data suggest that the late PPM displacement seems to be due to the continued global remodelling, rather than local remodelling in this area.

Left ventricular reverse remodelling

According to Stellbrink *et al.*, [18] we considered a decrease in LV end systolic volume >15% from baseline value as LVRR. In this fashion LVRR was observed, at late control, in 44.2% of patients with 10.3% showing further increment in ESV. Braun and co-workers[6] reported 60.5% of patients with significant reverse LV remodelling18 months after restrictive mitral annuloplasty. We had comparable results at 12-month follow-up (77.5%) but LVRR dramatically worsened at late controls. However, our data are not comparable because this group considered a 10% reduction in EDD as significant LVRR; however, measurements of LV volumes have been demonstrated to be more reliable than LV diameters in assessing LV remodelling, especially in enlarged ventricles.[29]

Predictors of recurrent mitral regurgitation

At multivariable model, ESV ≥ 145 mL, $SI_S \geq 0.7$, MPI ≥ 0.9, and WMSI ≥ 1.5 were predictors of recurrent MR. These results emphasize the importance of the extent of pre-operative LV global remodelling as having a central role in predicting inadequate results after UMRA. A new finding in this study is that MPI predicts the likelihood of MR, whereas LVEF was not significant. The MPI is a combined systolic and diastolic Doppler-derived index for the assessment of global LV performance which, differently from LVEF, is independent of LV loading conditions and heart rate.

Study limitation

Our study findings should be viewed in light of some inherent limitations.

1. Evaluation of LVRR was based on volumes obtained by echocardiography; volumetry by 2D echocardiography depends on geometric assumptions and is subject to image-plane positioning errors. Hence, it is not accurate in left ventricles that are distorted in shape such as after myocardial infarction. However, this limitation belongs to most of published paper regarding this pathology.
2. Viability testing was not performed in these patients. Therefore, lack of LVRR in non-responders might be also due to irreversible ischaemic myocardial damage (not viable myocardium). This issue deserves further investigation.
3. Postoperative evaluation of the coronary status was not assessed. It would have been helpful to differentiate between surgical failure (valve repair and CABG) and the progress of the coronary disease.
4. Fifteen patients with late deaths were not included in the study. They could have benefited from serial echocardiograms possibly with different results.
5. Estimated cut-offs are known to be very susceptible to changes in the study population. We employed bootstrapping techniques to validate the results, nonetheless, it has also been documented that the sensitivity/specificity associated with these cut-offs are overly optimistic.

Strength of the study

As far as we know, this is the largest cohort reported with UMRA in CIMR patients with detailed echocardiographic follow-up.

Table 5 Bivariate relationship of independent variables with recurrent mitral regurgitation

	MR+	MR−	P
Age	69.2 ± 6.4	67.8 ± 8.3	0.25
Male gender	98 (62.1)	38 (65.5)	0.9
NYHA class	3.2 ± 0.5	3.2 ± 0.5	0.74
CCS angina class	3.0 ± 0.3	3.1 ± 0.3	0.32
Euroscore			
Additive	7.9 ± 3.5	8.1 ± 4.6	0.66
Logistic	12.9 ± 6.3	12.8 ± 5.5	0.88
Hypertension	63 (39.9)	25 (40.3)	>0.9
Diabetes	51 (32.2)	17 (21.4)	0.49
COPD	21 (13.2)	7 (11.2)	0.71
Chronic renal disease	20 (12.6)	4 (6.5)	0.18
Cerebral vascular disease	10 (6.4)	4 (6.5)	0.9
Peripheral vascular disease	8 (5.1)	2 (3.3)	0.6
Familiar history	67 (42.4)	31 (50.0)	0.31
MI posterior/inferior	79 (50.0)	28 (45.1)	0.6
Grade of MR	3.0 ± 0.4	3.1 ± 0.4	0.1
Central direction of regurgitant jet	49 (31.0)	21 (33.8)	0.8
Annular dilatation	66 (41.7)	20 (32.2)	0.19
TA	3.3 ± 1.1	3.6 ± 1.2	0.06
ERO	38.3 ± 13	36.1 ± 11	0.09
RF	45.6 ± 11	44.7 ± 12	0.61
RV	57.4 ± 13	55.0 ± 10	0.25
CH	1.3 ± 0.2	1.1 ± 0.1	0.004
MA_s	4.1 ± 1.2	4.3 ± 1.2	0.3
MA_d	4.9 ± 1.2	5.2 ± 1.2	0.11
Number of diseased coronary vessels	2.5 ± 0.4	2.4 ± 0.4	0.11
Left main coronary artery	28 (17.7)	8 (12.9)	0.3
Pre-operative IABP	6 (3.7)	2 (3.2)	0.88
Ring size	27.6 ± 0.5	27.3 ± 0.9	0.21
Anastomoses/patient	2.2 ± 1.2	2.1 ± 1.0	0.51
Arterial Graft/patient	1.09 ± 0.1	1.06 ± 0.1	0.43
CCL time	124.4 ± 30	123.28	0.8
CPB time	92.7 ± 16	90.7 ± 18	0.61
EDD	65.1 ± 4	60.6 ± 5	0.003
ESD	53.9 ± 4	51.3 ± 3	0.01
LA dimensions	49.2 ± 7	50.3 ± 7	0.66
ESV	164.7 ± 23.9	131.2 ± 19.8	<0.001
EDV	215.3 ± 38.1	194.1 ± 39.2	0.09
LVEF	24.4 ± 7	34.1 ± 6	<0.001
MPI	0.90 ± 0.15	0.69 ± 0.17	<0.001
SI_S	0.74 ± 0.1	0.54 ± 0.1	<0.001
SI_D	0.80 ± 0.1	0.64 ± 0.09	0.002
WMSI	1.6 ± 0.2	1.1 ± 0.1	<0.001
PPM posterior D	2.4 ± 0.4	2.6 ± 0.5	0.2
APM posterior D	2.7 ± 04	2.9 ± 0.5	0.08
PPM lateral D	1.9 ± 0.4	2.0 ± 0.4	0.59
APM lateral D	1.3 ± 0.3	1.1 ± 0.2	0.008
PM_s separation	3.6 ± 0.5	3.6 ± 0.4	0.74
PPM fibrosa D	6.7 ± 0.6	6.6 ± 0.5	0.25
PPM WMSI	2.0 ± 0.1	2.2 ± 0.2	0.069
APM WMSI	1.3 ± 0.4	1.1 ± 0.3	0.04

MR+(−), presence (absence) of recurrent mitral regurgitation; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; MR, mitral regurgitation; MR, mitral regurgitation; CABG, coronary artery bypass grafting; TA, tenting area; ERO, effective regurgitant orifice; RF, regurgitant fraction; RV, regurgitant volume; CH, co-aptation heigh; MA_s, systolic mitral annular area; MA_d, diastolic mitral annular area; IABP, inta-aortic balloon pump; CPB, cardiopulmonary bypass; CCL, (aortic) cross-clamp; EDD, end diastolic diameter; ESD, end systolic diameter; LA, left atrium); ESV, end systolic volume; EDV, end diastolic volume; LVEF, left ventricular ejection fraction; MPI, myocardial performance index; SI_S, systolic sphericity index; SI_D, diastolic sphericity index; WMSI, wall motion score index; D, distance; PPM, posterior papillary muscle; APM, anterior papillary muscle; PMs, papillary muscles.

Furthermore, our patient cohort was more homogeneous than in other study:[30] All patients underwent associated CABG, they had no concomitant MV procedures, and the entire cohort was uniform regarding the MV ischaemic leaflet dysfunction. Moreover, to assess results for MV repair, we studied true 'recurrent'.

MR excluding those patients with 'residual 'MR in whom the insufficiency was presumably never eliminated at surgery. Additionally, we undertook valve sizing in a standardized fashion and the degree of undersizing was homogeneous over the 5-year-period of the study. Finally, we used only two rings (Carpentier's rigid or semi-flexible rings).

Clinical implications

In our experience, UMRA does not ensure successful and durable elimination of MR in all patients. Those who can benefit from combined UMRA and CABG should be pre-operatively identified utilizing echo predictors of recurrent MR. However, restrictive annuloplasty resulted to be ineffective in a large percentage of patients and results of this study suggest the need for different approaches directly addressing ventricular tethering in most of CIMR patients.[31–34] Such procedures may include LV plasty with volume reduction, chordal elongation or cutting, PM displacement, and leaflet elongation techniques as well as cardiac the employment of support devices introduced in recent years in clinical practice.[35,36] Mitral valve replacement, largely employed in the past in ischaemic regurgitation, although eliminates the short-term risk of recurrent MR, it is associated with poor long-term survival.[37] Thus, in our actual policy, we do not consider MV replacement as a reasonable alternative to repair.

Conclusions

Combined UMRA and CABG provided poor mid-term results with significant recurrent MR. Our findings emphasize the need for improved repair technique and better patient selection to identify patients with anticipated repair failure who could benefit more from valve replacement or other procedure directly addressing ventricular tethering. Long-term prospective studies on this controversial issue are encouraged.

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