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Original Article

Assessment of Left Ventricular Reverse Remodeling by Cardiac MRI in Patients Undergoing Repair Surgery for Severe Aortic or Mitral Regurgitation

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Objective: To evaluate left ventricular (LV) reverse remodeling after repair surgery for mitral regurgitation (MR) or aortic regurgitation (AR), aiming at determining optimal preoperative thresholds for normalization of LV volumes and function after surgery.
Design: Observational prospective cohort study.
Setting: Single-center, academic, tertiary care cardiovascular center.
Participants: Patients and volunteers.
Interventions: Cardiac magnetic resonance with measurement of indexed LV end-diastolic volume (LVEDVi) and end-systolic volume (LVESVi), mass (LVmassi), and ejection fraction (LVEF) was performed preoperatively and postoperatively.
Measurements and Main Results: The authors included 29 patients with AR and 59 patients with MR (46 ± 12 and 56 ± 12 years, follow-up 222 ± 57 days). Both AR and MR repair resulted in a significant reduction of LV volumes and mass (respectively, delta change in LVEDVi -55 mL/m^2 and -43 mL/m^2; in LVESVi -26 mL/m^2 and -10 mL/m^2; and in LVmassi -24 g/m^2 and -12 g/m^2; $p < 0.001$ for all).

Yet despite the absence of perioperative necrosis, 7 (24%) patients with AR had persistent LV dilatation (LVEDVi >106 mL/m^2) relative to controls and 16 (27%) patients with MR developed systolic LV dysfunction (LVEF <50%) postoperatively. Binary logistic regression analysis indicated preoperative LV volumes as the most accurate parameter for predicting both incomplete LV reverse remodeling in AR and LV dysfunction in MR. Receiver operating characteristic-determined thresholds were LVEDVi >155 mL/m^2 for AR and >129 mL/m^2 for MR.
Conclusion: Although both AR and MR repair allow significant reverse postoperative LV remodeling, persistent LV dilatation after AR correction and systolic LV dysfunction after MR repair are common and best predicted by increased preoperative LV volumes. This highlights the importance of considering LV volumes in the decision-making process.

Key Words: myocardial remodeling; valvular heart disease; cardiac magnetic resonance

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The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
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BOTH SEVERE chronic aortic regurgitation (AR) and mitral regurgitation (MR) induce left ventricle (LV) volume overload and result in dilatation and eccentric remodeling,[1,2] progressively leading to LV dysfunction that impairs patients' survival.[3] Surgical correction of the regurgitation results in reversal remodeling with substantial decrease of LV dilatation after surgery.[1,4–6] Because persistent LV dilatation or dysfunction has been associated with worse long-term outcome, ideally surgery should be timed to aim at normalizing postoperative LV volumes and function. However, optimal timing of surgery in AR and MR remains controversial, even more with the advent of valve repair, and it is unclear what the predictors of incomplete reverse remodeling are.

Because of its high precision and reproducibility in measurement of LV volumes and mass, cardiac magnetic resonance (CMR) is the optimal technique for studying LV remodeling in patients with valve disease. It also may detect fibrosis/necrosis, which could be potential confounders explaining incomplete postoperative remodeling.

In the present work, the authors thus sought to study LV remodeling using CMR in patients operated on relatively early in the course of AR or MR in order to accomplish the following: (1) compare remodeling as assessed by changes in LV volumes and mass caused by both conditions; (2) assess if all patients reach postoperative normal values (as defined by reference values of healthy volunteers) of LV volumes and function, and if not; (3) identify potential predictors and thresholds of incomplete (ie, not reaching normal values of reference values of healthy subjects) postoperative LV reverse remodeling.

Methods

Study Population

Patients hospitalized in the authors' center between February 2005 and November 2013 for surgery of isolated chronic severe primary AR or MR and assessed by CMR preoperatively and 6 to 12 months postoperatively were eligible. The study was approved (2011/02NOV/42 and 2010/26FEV/061) by the institutional review board of the authors' institution, and subjects were included after giving written informed consent to participate in this study. The authors only included asymptomatic or paucisymptomatic (New York Heart Association [NYHA] class I or II) patients with successful uncomplicated surgery. The authors excluded patients requiring prosthetic valve implantation, with periprocedural infarction (defined as new late-gadolinium enhancement [LGE] by CMR), or with postoperative residual regurgitation ≥ grade 2 on 2-dimensional transthoracic echocardiography (TTE). The authors also excluded those with preoperative overt LV dysfunction, significant coronary artery disease (CAD) (ie, stenosis >70% or subendocardial necrosis at LGE by CMR), atrial fibrillation, prior cardiac surgery, concomitant other valvular disease grade ≥2, rheumatic disease, or suboptimal image quality for adequate analysis. Hence 127 patients were considered for inclusion, and 88 patients were retained for analysis in this study (Fig. 1). Patients were compared against a control group of 30 healthy asymptomatic age- and sex-matched volunteers, recruited by advertisement in the local community (normal rest electrocardiogram (ECG), normal TTE, and cardiac computed tomography without significant CAD for those >44 years old). The authors adhered to Strengthening The Reporting of Observational Studies in Epidemiology guidelines for the reporting of this study.

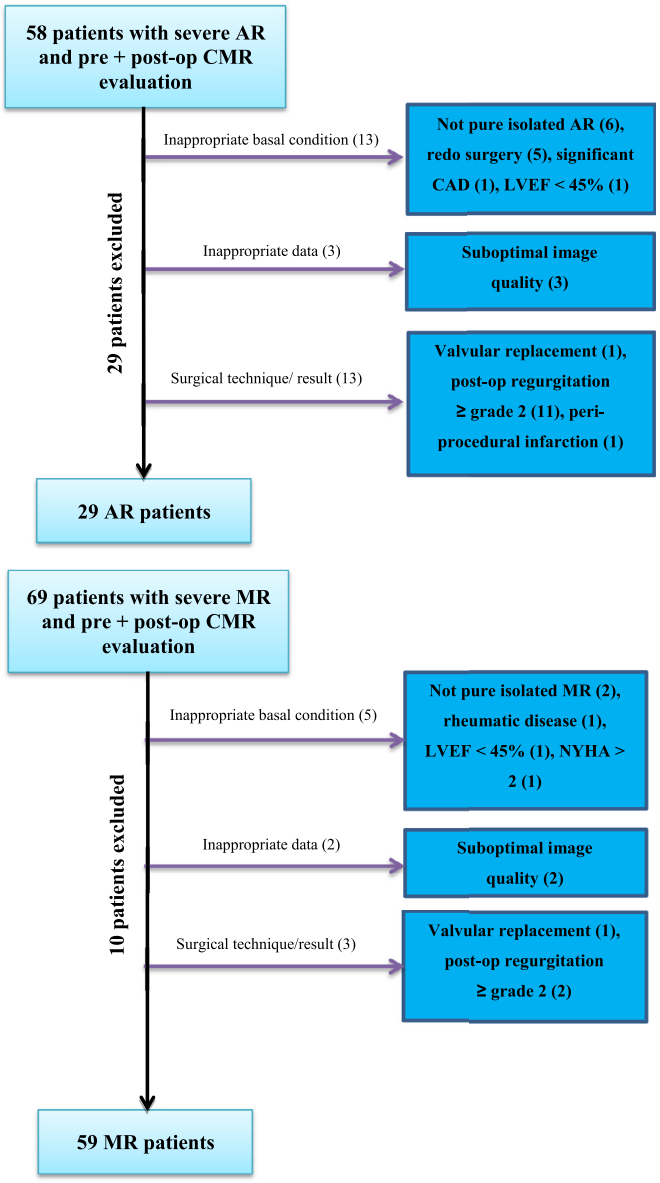

Fig 1. Flowchart illustrating patients' inclusion/exclusion. AR, aortic regurgitation; CAD, coronary artery disease; CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association.

CMR Image Acquisition and Analysis

CMR was performed on a 1.5-T system (Intera CV, Philips Medical System, Best, Netherlands) as previously described.[7] Briefly, 10 to 12 consecutive short-axis images covering the entire LV, and respectively one 2-, 3-, and 4-chamber long-axis images were acquired using an ECG-gated breath-hold cine steady-state free precession sequence to allow assessment of myocardial function and mass. Identical prescriptions were

acquired 10 to 15 minutes after injection of 0.2 mmol/kg of gadolinium-based contrast agent for the assessment of LGE. Quantitative through-plane measurements using ECG-gated phase-contrast velocity sequence at the level of the sinotubular junction (real-time respiratory triggered acquisition) were performed. Images were analyzed using a dedicated Philips workstation (ViewForum, Philips Medical Systems) and free-of-charge software Segment version 1.9 (http://segment.heiberg.se). LV end-diastolic and end-systolic volumes (LVEDV and LVESV), LV ejection fraction (LVEF), and LV mass were obtained by manual tracing of contours on the short-axis images at end-diastole and end-systole (Simpson's method), with trabeculations and papillary muscles included in volumes. Myocardial density was assumed to be 1.05 g/cm^3. Because LV dimensions are dependent on body size, measurements were indexed (i) for body surface area (Gehan and George formula). Aortic regurgitant volume was determined by reversal flow during diastole, and mitral regurgitant volume was computed as the difference between LV stroke volume (determined by endocardial segmentation) and aortic forward volume by phase-contrast imaging. Posterior (inferolateral) LV wall thickness, LV end-diastolic diameter (LVEDD), and LV end-systolic diameter (LVESD) were measured on 3-chamber view, and LV end-diastolic long-axis length measured as the longest from 4- and 2-chamber views.

The following indexes were computed[7,8]:

$$\text{Relative wall thickness} = \frac{2\,PWd}{LVEDD}$$

$$\text{LV sphericity index} = \frac{LVEDL}{LVEDD}$$

End systolic meridional wall stress :

$$\sigma m = 1.33\,\frac{pLVESD}{2PWs\left(1+\frac{PWs}{2LVESD}\right)}\,(\text{kdyn/cm}^2)$$

where p = systolic blood pressure, *d* refers to a measurement performed at end-diastole and *s* at end-systole, and 1.33 is a conversion factor.

Echocardiographic Data

A standardized complete comprehensive echocardiographic examination, including M-mode, 2-dimensional echocardiography, and Doppler examinations, was performed using a Sonos 5500 or iE33 echocardiograph (Philips Medical Systems, Andover, MA) equipped with a 3.5/1.75-MHz phased-array transducer. All tests were conducted by experienced sonographers. For the purpose of the present study, all preoperative echocardiographic images were reanalyzed offline on Xcelera 1.2 LF 4 (Philips Medical Systems) workstations by 2 observers (S.S. and S.P.), who were blinded to the preoperative and follow-up clinical and CMR data at the time of analysis. Analysis was performed according to established guidelines. Measurements of LV diameters were performed on 2D echocardiographic images from parasternal long-axis view, and LV volumes were computed by biplane Simpson's method as recommended.[9] Severity of valvular regurgitation was assessed with a multiparametric approach as recommended,[10–12] and for the purpose of the study the authors reported effective regurgitant orifice and regurgitant volume values computed by proximal isovelocity surface area technique as it best correlates with CMR quantification of regurgitation.[13]

Statistical Analysis

Statistical analysis was performed using NCSS version 07.1.18 (NCSS, Kaysville, UT) software. Continuous variables were expressed as mean ± standard deviation, and categorical variables as counts and percentages. Comparison of continuous variables was made using Student *t* test for 1 or 2 samples where appropriate for comparison between 2 variables, and 1-way analysis of variance for comparison of more than 2 variables. If significant for comparison of >2 groups, identification of between-groups difference was assessed by Kruskal-Wallis Z-test. Values in subjects were considered normalized when they were within a 95% confidence interval of age-matched volunteers.

Linear regression was assessed by Pearson's coefficient of correlation. Categorical variables and proportions were compared using χ^2 test or Fisher exact test where appropriate. Logistic regression analysis was performed in a binary fashion. The identification of the best threshold value was determined with the use of receiver operating characteristic (ROC) curves and Youden index. All tests were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

Patients' Characteristics

The authors included 29 patients with severe AR and 59 with severe MR. Baseline characteristics are listed in Table 1. Quantification of regurgitation was feasible in 27 of 29 and 58 of 59 patients by TTE, and in 28 of 29 and 59 of 59 by CMR. The mechanism of AR was aortic root dilation for 6 and valvular lesion for the remaining 23 (21 prolapse of which 15 were associated with bicuspid disease, 1 quadricuspid valve, and 1 endocarditis sequelae). The mechanism of MR was degenerative valve prolapse for 57 (45 involving posterior, 4 anterior leaflet, and 8 bileaflet; 23 flail leaflets) and endocarditis sequelae and posterior mitral cleft in 1 patient, respectively.

Valve Surgery

Among patients with AR, 20 underwent combined Tirone David root surgery associated with aortic valve repair, 5 subcommissural annuloplasties, 2 external annuloplasties, and 2 Ross procedures. All patients with MR underwent mitral annuloplasty (12 by heartport access); in 7 patients tricuspid annuloplasty was associated (institutional study, no significant lesion). All procedures were uncomplicated.

Table 1
Baseline Characteristics of Patients

		AR (n = 29)	MR (n = 59)	Controls (n = 30)
Clinical data	Age (y)	46 ± 12*	56 ± 12*	51 ± 15
	Male (%)	27 (93)	49 (83)	22 (73)
	Height (cm)	177 ± 7	176 ± 9	175 ± 7
	Weight (kg)	83 ± 15‡	78 ± 13	72 ± 8‡
	BSA (m^2)	2.02 ± 0.20	1.96 ± 0.19	1.88 ± 0.14
	HTN (%)	16 (55)§	18 (31)§	2 (7)§
	Diabetes (%)	0	0	2 (7)
	NYHA class I/II/III/IV	20/9/0/0	29/30/0/0	30/0/0/0‖
2D TTE data	LVEDD (mm)	63 ± 5§	57 ± 5§	48 ± 4§
	LVESD (mm)	44 ± 6§	35 ± 5§	32 ± 4§
	LVEDVi (mL/m^2)	119 ± 22§	92 ± 22§	56 ± 10§
	LVESVi (mL/m^2)	49 ± 11§	34 ± 9§	23 ± 5§
	ReV (mL)	73 ± 28	81 ± 30	-
	ERO (mm^2)	32 ± 13†	54 ± 21†	-
CMR CMR data	ReV (mL)	52 ± 21†	69 ± 36†	-
	RF (%)	38 ± 13	44 ± 15	-

NOTE. Controls with diabetes had HbA1C <6.5% with metformin as sole treatment.
Abbreviations: ANOVA, analysis of variance; AR, aortic regurgitation; BSA, body surface area; CMR, cardiac magnetic resonance; ERO, effective regurgitant orifice; HTN, hypertension; i, value indexed for body surface area; LV, left ventricle; LVEDD, LV end-diastolic diameter; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVESV, LV end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; ReV, regurgitant volume; RF, regurgitant fraction; TTE, transthoracic echocardiography.
* = $p < 0.01$, AR different from MR by ANOVA.
† = $p < 0.05$, AR different from MR by Student *t* test.
‡ = $p < 0.01$, AR different from controls by ANOVA.
§ = $p < 0.001$, all groups statistically different by ANOVA.
‖ = $p < 0.001$, controls different from AR and MR patients.

LV Remodeling and Postoperative Changes

Global Changes

Follow-up postoperative CMR was performed at 222 ± 57 days. Preoperative and postoperative hemodynamic and LV remodeling parameters by CMR are shown in Table 2. Preoperatively, systolic blood pressure was increased and diastolic pressure decreased in patients with AR, but meridional wall stress was similar. Postoperatively, blood pressure normalized in AR and wall stress decreased.

Preoperatively, both patients with AR and MR presented significantly enlarged ventricles and higher LV mass than controls. Despite a similar magnitude of regurgitant volume by TTE, the increase in LV volumes and mass was greater in patients with AR, with lower EF.

Individual changes of LVEDVi, LVESVi, $LVmass_i$, and LVEF after AR and MR surgery are shown in Figure 2. Both patient groups presented significant regression of volumes and mass after surgery ($p < 0.001$ for all). Average postoperative LVEDVi and LVESVi were no more statistically different compared to the control group, while $LVmass_i$ remained significantly enlarged in AR patients.

Individual Changes

Yet on an individual basis, when considering normalization as reaching a value <95% confidence intervals of controls (ie, LVEDVi <106 mL/m^2, LVESVi <47 mL/m^2, $LVmass_i$ <70 g/m^2 based on the authors' population), the authors noted persistent dilatation of LVESVi in 10 of 59 patients with MR, and of both LVEDVi and LVESVi in 7 of 29 patients with AR. $LVmass_i$ normalized to 95% confidence intervals of healthy volunteers in all but 2 patients after MR repair, but remained significantly increased relative to healthy volunteers in 13 of 29 after AR surgery.

LVEF remained unchanged in patients with AR (54 ± 6% *v* 55 ± 6 %, $p = 0.20$) while it significantly decreased after MR surgery (61 ± 6% *v* 53 ± 7 %, $p < 0.001$). Postoperative LVEF was within normal values of healthy volunteers (ie, ≥50%) in all but 3 patients undergoing surgery for AR, but was abnormal in 16 of 59 patients after MR repair. Proportions of patients reaching normal range are shown in Figure 3.

Remodeling parameters (variation in $LVmass_i$, LVEDVi, and LVESVi) were correlated strongly between each other, but not with variation in LVEF.

Predictors of Poor Postoperative LV Reverse Remodeling

Given that the authors observed incomplete reverse remodeling with persistent LV dilatation (ie, LV dimensions greater than normal reference values in healthy volunteers) in 24% of patients with AR and development of LV systolic dysfunction in 27% of patients after MR repair, the authors attempted to determine the preoperative predictors for such poor postoperative outcomes and listed univariate and multivariate predictors for persistent LV dilatation in AR and for development of LV systolic dysfunction after MR surgery in Tables 3 and 4.

Multivariate logistic regression identified preoperative LVEDVi as the sole predictor for incomplete remodeling (risk

Table 2
LV Remodeling: Pre- and Postoperative CMR Values, Comparison With Controls

		AR (n = 29)	Controls (n = 30)	MR (n = 59)
sBP (mmHg)	Preop	139 ± 16*	125 ± 13	131 ± 15
	Postop	129 ± 15		129 ± 15
dBP (mmHg)	Preop	69 ± 10*	78 ± 8	79 ± 9
	Postop	82 ± 9		80 ± 10
HR (bpm)	Preop	66 ± 13	62 ± 10	67 ± 12
	Postop	68 ± 13		73 ± 11†
LVEDVi (mL/m^2)	Preop	148 ± 32*	84 ± 11	124 ± 26*
	Postop	93 ± 16		81 ± 13
LVESVi (mL/m^2)	Preop	69 ± 18*	35 ± 6	49 ± 13*
	Postop	43 ± 10		39 ± 10
LVEF (%)	Preop	54 ± 6‡	58 ± 4	61 ± 6
	Postop	55 ± 6		53 ± 7†
LVmass$_i$ (g/m^2)	Preop	94 ± 19§	49 ± 11	66 ± 15*
	Postop	70 ± 11§		54 ± 9
Mass/volume (g/mL)	Preop	0.64 ± 0.11	0.58 ± 0.10	0.54 ± 0.09
	Postop	0.75 ± 0.11†		0.68 ± 0.11†
RWT	Preop	0.27 ± 0.05§	0.31 ± 0.06	0.27 ± 0.05*
	Postop	0.35 ± 0.06†		0.31 ± 0.06
Sphericity index	Preop	1.71 ± 0.15	1.81 ± 0.17	1.63 ± 0.17§
	Postop	2.00 ± 0.22†		1.93 ± 0.25§
σ_m (kdyn/cm^2)	Preop	223 ± 54	197 ± 43	178 ± 64
	Postop	155 ± 40†		197 ± 66

NOTE. Comparisons were made separately for each group, using ANOVA followed by Kruskal-Wallis Z-test to compare patients' pre- and postoperative values with controls.

Abbreviations: ANOVA, analysis of variance; AR, aortic regurgitation; BP, blood pressure (d for diastolic and s for systolic); BSA, body surface area; CMR, cardiac magnetic resonance; HR, heart rate; i, value indexed for body surface area; LV, left ventricle; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; MR, mitral regurgitation; RWT, relative wall thickness; σ_m, meridional wall stress at end-systole.

* $p < 0.005$, preoperative value different from postoperative value and control group.

† $p < 0.001$, postoperative value different from preoperative value and control group.

‡ $p = 0.008$, preoperative value different from control group.

§ $p < 0.001$, all groups (preoperative, postoperative and controls) different from each other.

ratio 1.08 for 1 mL/m^2) in AR patients. ROC analysis demonstrated with an area under curve (AUC) of 0.90 that LVEDVi >155 mL/m^2 had 100% sensitivity and 68% specificity for predicting incomplete remodeling.

For MR repair, LVESVi was the best predictor for persistent abnormal postoperative LV function (risk ratio 1.07 for 1 mL/m^2), whereas AUC by ROC analysis was slightly better for LVEDVi (AUC = 0.75 for LVEDVi >129 mL/m^2 with a 72% sensitivity and 76% specificity, *v* AUC = 0.73 for LVESVi >60 mL/m^2 with 50% sensitivity and 95% specificity).

Interobserver Variability of CMR Measurements

Interobserver reproducibility was assessed in 71 patients with excellent intraclass correlation coefficient of 0.91 for LVmass, 0.96 for LVEDV, 0.93 for LVESV, and 0.79 for LVEF

Follow-up

The authors tried to obtain follow-up information in the study's patients by contacting them, their general practitioner, or their cardiologist.

In AR, follow-up was 100% complete for vital status (mean follow-up 82 months, range 29-116). Two patients died: 1 from lung cancer and 1 from cerebral hemorrhage, respectively, 44 and 36 months after intervention. Another patient needed redo surgery after 50 months for endocarditis, and received aortic valve replacement. Symptomatic status was obtained for 26 of 27 alive patients: all were in NYHA class I, except 1 in class II (an 89-year-old man with flutter arrhythmia). Echocardiographic data at follow-up were available for 20 of 29 patients: light LV dilation was mentioned for 7 (including 1 deceased patient) and moderate dilation for 2 (including the one with redo surgery).

Follow-up in MR was also 100% complete for vital status (mean follow-up 91 months, range 36-164). One patient died 64 months after surgery (hospitalized for left atrial thrombus with multiple embolisms, unexpected sudden death while recovering after the acute phase). No redo intervention was reported. Symptomatic status was obtained for 57 of 58 patients: 4 of them were in NYHA class II (others in class I). Echocardiographic data were available in 39 of 59 patients: alteration of LVEF was reported in 2 (predominantly visual evaluation, some Teichhloz's formula, no Simpson reported).

Discussion

The authors' study used CMR to allow precise assessment of LV remodeling in patients with AR and MR and to study its reversal after repair surgery, as use of volumes has been proven

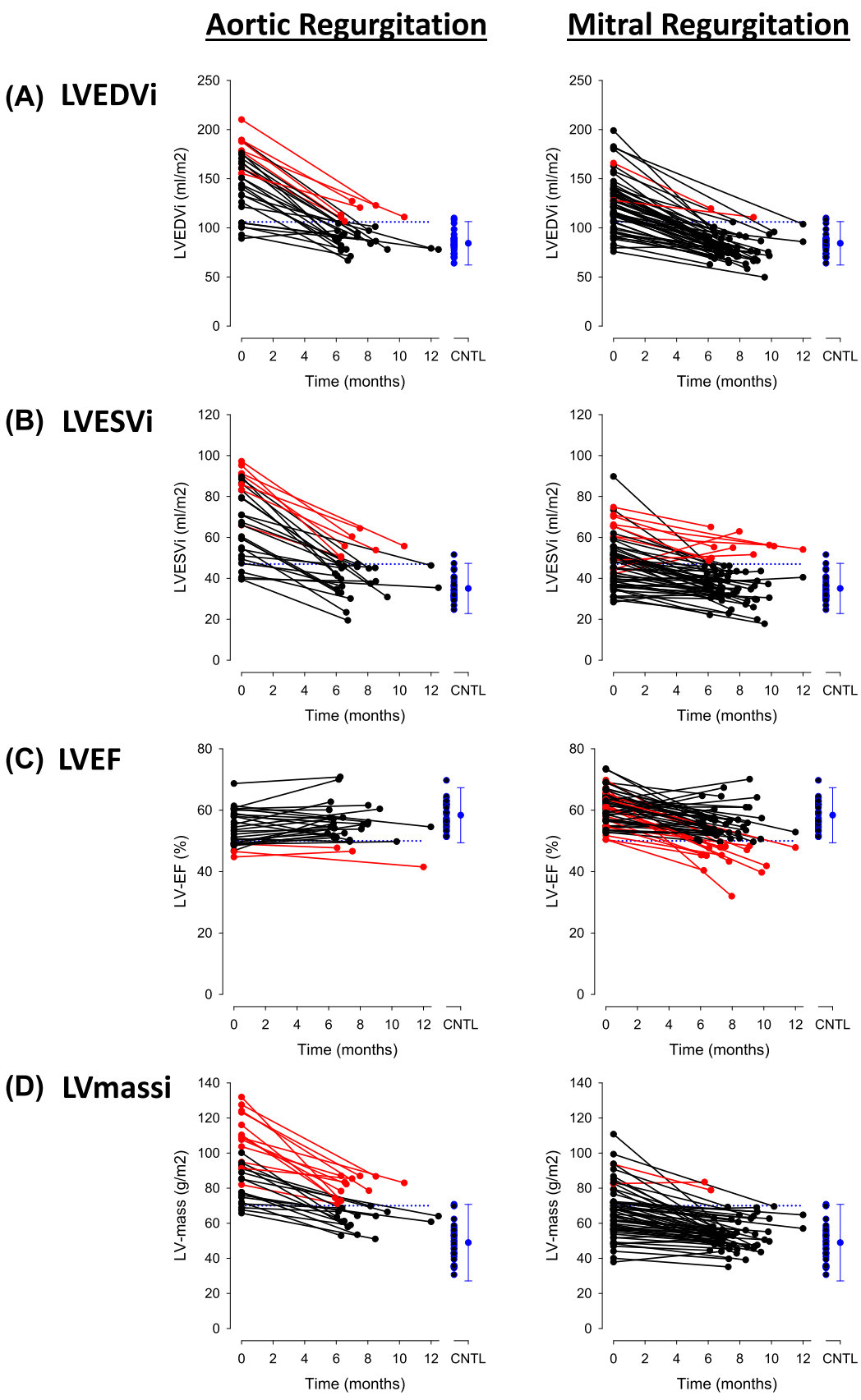

Fig 2. Individual changes between preoperative and postoperative values in patients with aortic and mitral valve regurgitation. (A) LV end-diastolic volume indexed. (B) LV end-systolic volume indexed. (C) Ejection fraction. (D) LV mass indexed. *Blue points* indicate values of healthy controls, and *blue dotted line* shows the upper 95% limit of these normal values in healthy controls. *Black lines* indicate patients returning to normal values after surgery; *red lines* indicate individuals which fail to return to normal values after surgery. CNTL, controls; LVEDVi, left ventricular end-diastolic volume indexed for body surface area; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume indexed for body surface area; $LVMass_i$, left ventricular mass indexed for body surface area.

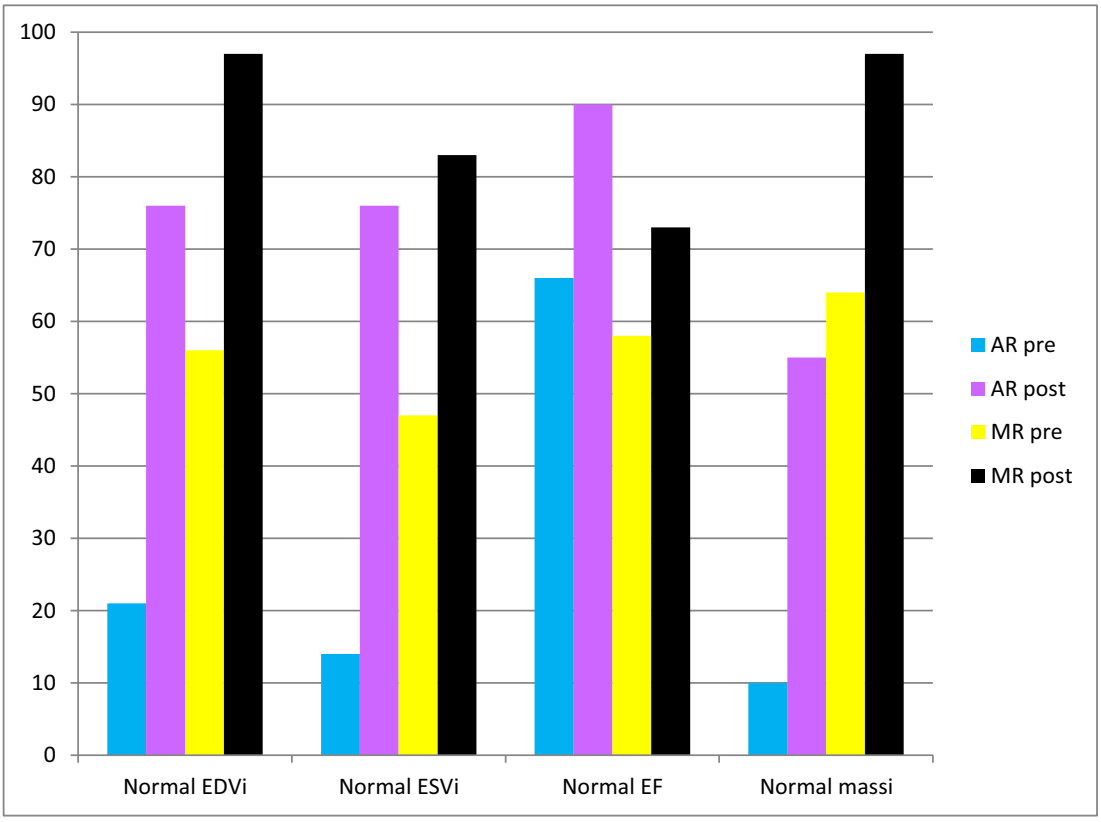

Fig 3. Percentage of patients reaching normal values. AR post, postoperative values of aortic regurgitation patients; AR pre, preoperative values of aortic regurgitation patients; EF, ejection fraction; LVEDVi, left ventricular end-diastolic volume indexed for body surface area; LVESVi, left ventricular end-systolic volume indexed for body surface area; $LVMass_i$, left ventricular mass indexed for body surface area; MR post, postoperative values of mitral regurgitation patients; MR pre, preoperative values of mitral regurgitation patients.

superior to linear dimensions, particularly for enlarged LV[14] and valvular regurgitation conditions.[7] The authors studied a homogenous group of patients with lone valvular heart disease predominantly treated by valve repair, free of other conditions such as CAD or significant residual regurgitation, which potentially could interfere with LV remodeling. Also, all patients were without signs of advanced heart failure (no NYHA class >II nor LVEF <45% in AR or <50% in MR) prior to surgery. The salient findings of the authors' study can be summarized as follows:

- LV remodeling assessed by CMR differs in chronic AR and MR.
- Successful repair resulted in significant reverse remodeling 6 to 12 months post-surgery.
- Despite relative early surgery, after AR repair 24% of patients did not normalize LV volumes (45% for $LVmass_i$), whereas 27% of patients with MR developed systolic dysfunction with LVEF <50% postoperatively.
- The most accurate predictor for suboptimal postoperative outcome was excessive preoperative LV dilatation as measured by LV volumes for both conditions.

LV Remodeling in AR Versus MR

Although both AR and MR are characterized by LV volume overload leading to LV eccentric remodeling, MR differs fundamentally from AR in that in MR, the volume-loaded LV faces relatively low impedance to outflow and normal or subnormal afterload, whereas in AR afterload is increased.[15] Therefore, as confirmed by the authors' present study, the LV remodels differently with higher LV volumes, mass, and also mass/volume ratio in AR, allowing to withstand the increased afterload and wall stress. Increased LVEF in chronic MR is explained by the low afterload state: ejection may remain preserved falsely for a long duration even when myocardial dysfunction is established, because LV alteration in contractility initially is compensated by modified loading conditions.[16] There are few studies directly comparing AR and MR, but their results match the current study.[17–19]

Surgical Valve Repair and Reverse Remodeling After AR and MR Correction

In the present study, the authors consistently used valve repair to correct the underlying disease in MR, and in most of AR repair (2 Ross procedures, the authors considered autograft as equal to repair for myocardial recovery: no valvular stent or prosthetic material interfering with myocardial dynamics). For degenerative MR, the use of valve repair is a well-established technique with low mortality[20] and durable results,[21] and is currently the method of choice in the guidelines. Also, mitral valve repair has been shown to provide better functional outcome and survival than valve replacement.[22] Although AR

Table 3
Clinical, Echocardiographic, and CMR Predictors of Postoperative Normalization of LVEDVi in Patients With AR—Logistic Regression

		Univariate		Multivariate	
		RR (95% CI)	p value	RR (95% CI)	p value
Clinical parameters	Age	0.99 (0.93-1.06)	0.85		
	Sex	-	-		
	BSA (m^2)	0.16 (0.01-15.33)	0.43		
	NYHA class II	1.99 (0.34-11.63)	0.44		
TEE param	ERO (mm^2)	0.92 (0.85-1.01)	0.08		
	ReV (mL)	0.99 (0.95-1.02)	0.38		
CMR parameters	LVEDVi (mL/m^2)	1.08 (1.01-1.16)	0.02	1.08 (1.01-1.16)	0.02
	LVESVi (mL/m^2)	1.14 (1.02-1.27)	0.02		
	$LVmass_i$ (g/m^2)	1.06 (1.00-1.12)	0.04		
	LVEF (%)	0.89 (0.74-1.06)	0.20		
	LVEDDi (mm/m^2)	1.36 (0.98-1.87)	0.06		
	LVESDi (mm/m^2)	1.20 (0.92-1.57)	0.18		
	σ_m ($kdyn/cm^2$)	1.00 (0.99-1.02)	0.87		
	ReV (mL)	1.03 (0.98-1.07)	0.27		
	RF (%)	0.99 (0.94-1.06)	0.96		

Abbreviations: AR, aortic regurgitation; BSA, body surface area; CI, confidence interval; CMR, cardiac magnetic resonance; ERO, effective regurgitant orifice; $_i$, value indexed for body surface area; LV, left ventricle; LVEDD, LV end-diastolic diameter; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVESV, LV end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; ReV, regurgitant volume; RF, regurgitant fraction; RR, risk ratio; TEE, transthoracic echocardiography; σ_m, meridional wall stress at end-systole.

valve repair is still less established, in expert centers it provides durable results and improved survival compared to valve replacement, with very low operative mortality rate.[23,24] In the authors' study, by design all patients underwent successful correction of their underlying disease: the authors carefully excluded patients with suboptimal repair, because persistent significant regurgitation has been associated with incomplete reverse remodeling.[1,25] The authors also excluded other confounding factors of incomplete reverse remodeling, such as perioperative necrosis by LGE-CMR.

The authors observed that surgical correction of the volume overload associated with AR or MR resulted in a significant reduction of LV mass and volumes, reflecting a positive reverse remodeling in patients. These findings are concordant with previous studies.[1,7,25–28] However, the authors' use of CMR and the comparison to an age-matched control group

Table 4
Clinical, Echocardiographic, and CMR Predictors of Postoperative Normalization of LVEF in Patients With MR—Logistic Regression

		Univariate		Multivariate	
		RR (95% CI)	p value	RR (95% CI)	p value
Clinical parameters	Age	0.98 (0.93-1.02)	0.33		
	Sex	3.97 (0.46-30.84)	0.21		
	BSA (m^2)	1.54 (0.08-30.84)	0.78		
	NYHA class II	1.35 (0.42-4.27)	0.61		
TEE param	ERO (mm^2)	1.01 (0.99-1.03)	0.33		
	ReV (mL)	1.01 (0.99-1.03)	0.42		
CMR parameters	LVEDVi (mL/m^2)	1.03 (1.01-1.06)	0.009		
	LVESVi (mL/m^2)	1.07 (1.02-1.13)	0.009	1.07 (1.02-1.13)	0.009
	$LVmass_i$ (g/m^2)	1.05 (1.01-1.10)	0.02		
	LVEF (%)	0.94 (0.84-1.05)	0.27		
	LVEDDi (mm/m^2)	1.11 (0.95-1.29)	0.18		
	LVESDi (mm/m^2)	1.21 (1.02-1.44)	0.03		
	σ_m ($kdyn/cm^2$)	1.01 (1.00-1.02)	0.12		
	ReV (mL)	1.02 (1.00-1.04)	0.01		
	RF (%)	1.05 (1.00-1.09)	0.05		

Abbreviations: BSA, body surface area; CI, confidence interval; CMR, cardiac magnetic resonance; ERO, effective regurgitant orifice; $_i$, value indexed for body surface area; LV, left ventricle; LVEDD, LV end-diastolic diameter; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVESV, LV end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; ReV, regurgitant volume; RR, risk ratio; TEE, transthoracic echocardiography; σ_m, meridional wall stress at end-systole.

allowed more detailed analysis than prior works. In particular, the authors were able to observe that despite relative early surgical correction, this reverse remodeling did not allow a complete normalization of LV parameters in all patients. More importantly, the type of reverse remodeling differed significantly between AR and MR.

Indeed, in AR repair the authors observed that despite reduction of afterload and wall stress, reverse remodeling with reduction of LV mass and volumes occurred only partially. Although all patients presented a reduction of LV mass and volumes, 24% did not return to normal LV volumes as compared to controls, and 45% regarding LV mass. This finding is novel and has not been described previously. In their study, Brown et al. mentioned that mass did not reach normal value postoperatively, but did not give individual information nor compare to a control group.[29] The presence of significantly higher systolic blood pressure values among AR patients might be a confounder for increased LVmass (at least preoperatively, as values normalized at postoperative evaluation). But the similar relative wall thickness compared to MR patients, indicating eccentric rather than concentric hypertrophy, and the absolute systolic mean value <140 mmHg are not supportive of a significant effect of blood pressure on results.

LV volumes and mass mainly normalized after MR repair; however. LVEF decreased and a substantial proportion of patients developed LV dysfunction. A postoperative fall in LVEF was expected according to the change in loading conditions,[16] besides already being observed in other studies[5,6,27]; but the proportion of fall eventually resulting in LV dysfunction (the decrease in preload and increase in afterload unmasking latent ventricular dysfunction) among the authors' population was surprisingly high. Effectively, Matsumura et al. depicted in their study an occurrence of LV dysfunction in 9% of patients with preoperative LVEF 55% to 59%, and 8% for those ≥60%.[5] Yet the study by Quintana et al. was closer to the present study, with 22% of patients without class I or IIa indication for surgery developing LV dysfunction postoperatively.[30]

Predictors of Incomplete Remodeling and Clinical Implications

The authors subsequently evaluated the predictors of poor LV reverse remodeling after both AR and MR surgery.

In both conditions, increased LV volumes were the most powerful predictor for adverse remodeling, exceeding LV dimensions likely because they reflect more accurately the extent of LV remodeling, indicating that this parameter should be preferred in assessment of severity of valve disease. The cutoff value of LV volumes for optimal prediction of adverse outcome was, however, different for both diseases (higher for AR), concordant with the authors' prior observation that degree of remodeling depends on affected valve. The best parameter by ROC was LVEDVi for both conditions, and indeed Uretsky et al. already demonstrated that it had the best correlation with regurgitant volume,[18] and thus severity of the disease. LVEDVi and LVESVi were correlated strongly. Unlike some previous studies, the authors did not find preoperative LVEF affecting the fate of patients with MR, probably because none had overt LV dysfunction at baseline.

The authors tried to assess if the definition of LV alteration used in guidelines was predictive of postoperative evolution in the authors' patients. According to guidelines, asymptomatic patients should be offered intervention if they present LV dilation (defined as LVESD >40 mm for MR and LVESD >50 mm and/or LVEDD >65 mm for AR in American College of Cardiology/American Heart Association guidelines,[11] and LVESD >45 mm for MR and LVESD >50 mm and/or LVEDD >70 mm for AR in European Society of Cardiology guidelines) and/or systolic dysfunction (LVEF <60% for MR or <50% for AR in both guidelines) based on TTE. The authors found that reaching guidelines' thresholds (or not) was not predictive of postoperative evolution.

This study only considered patients referred for surgery, and did not compare regurgitation assessment between CMR and echocardiography. Previous studies, however, demonstrated that correlation of valvular regurgitation quantification by CMR versus by echo was moderate and worse in patients with eccentric, late systolic, or multiple jets;[31] and that regurgitant volume or fraction as assessed by CMR was correlated better to postoperative LV remodeling,[6] and was more efficient in predicting patients' outcome (ie, evolution to guidelines indicated surgery or mortality).[31–33] Considering the better predictive value of CMR and the guidelines recommendation to propose surgery in selected asymptomatic patients with severe MR, there is rising concern about the role of CMR in clinical decision-making in referring patients for surgery.[34]

Study Limitations

This was a single-center study with a relatively limited number of patients. However, performance of the exams and analysis by the same machines and operators should allow better homogeneity and reproducibility.

The endpoint assessed in this study was reverse remodeling of LV dimensions and function, but not outcome data: assessment of potential clinical repercussion of these observations would certainly require a long follow-up period in these low-risk patients. However, other studies with more heterogeneous patients groups demonstrated correlation between outcomes and severity of LV remodeling.[4,25,26,28]

This study only considered patients with surgery performed relatively early; results thus may not be inferred for patients with actual symptoms of valvular disease.

The authors' postoperative measurements were obtained 6 to 12 months after surgery; one cannot exclude that reverse remodeling might continue further until a more complete recovery. However, previous studies with sequential

assessment demonstrated that most of the regression in volumes occurs very early after intervention, with few variations in long term, especially for patients with preserved preoperative LV function.[25–27,35] There are, though, less data concerning LV mass. Also, the authors' analysis of the predictors of reverse remodeling did not show any influence of the delay from surgery to follow-up on the authors' results.

The authors did not use invasive measurements of LV pressures, as they are not performed routinely, so the authors could only approximate end-systolic wall stress and had no assessment of end-diastolic wall stress. This limits the interpretation of hemodynamic influence on the authors' results.

Conclusion

This study demonstrated that although both AR and MR repair allow significant reverse postoperative LV remodeling, persistent LV dilatation after AR correction and systolic LV dysfunction after MR repair are common, even among patients without overt preoperative complication. Adverse remodeling was best predicted by preoperative LV dilatation. This supports the use of LVEDVi and LVESVi as indicators of severity of valve disease rather than 2D measurements. This highlights the importance of considering LV volumes in the decision- making process.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2018.11.013.

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