echocardiographic studies did not describe problems with functional MS or ring PPM after mitral valve repair using an undersized annuloplasty ring.[3,4]

Magne et al[5] also found that this hemodynamic consequence (functional MS) may be associated with residual pulmonary hypertension (PH) after RMA. However, little data from invasive hemodynamic monitoring techniques with regard to functional MS have been reported. The purpose of this study was to evaluate the post-RMA hemodynamic data, to determine whether stringent RMA for functional MR results in functional MS, and whether this hemodynamic consequence is mainly responsible for residual PH after the operation. We also attempted to determine factors predicting residual PH and short-term outcome in patients undergoing the RMA procedure.

Methods

Patients

Between July 2003 and November 2009, 195 patients underwent RMA for functional MR using a semirigid complete ring (Carpentier-Edwards Physio ring; Edwards Lifesciences, Irvine, CA) at 3 university-affiliated hospitals. Functional MR associated with cardiomyopathy was defined as a combination of moderate-to-severe MR with (1) a history of at least 1 hospitalization for heart failure in the previous 6 months, despite maximal medical treatment, (2) global LV dysfunction (LV ejection fraction <40%) with a significantly enlarged left ventricle, and (3) type IIIb leaflet dysfunction, according to Carpentier classification. Of these patients, 87 were excluded because of concomitant surgical ventricular reconstruction (n=69), redo mitral valve surgery owing to MR recurrence (n=4), postoperative infective endocarditis (n=2), or early hospital death (n=12). The final study population consisted of 108 patients (86 men, 22 women), who had a mean body surface area (BSA) of 1.65±0.19 cm^2 (range, 1.30 to 2.26). Because the patients with a 26-mm Physio ring had a larger BSA than those with a 24-mm Physio ring, patient baseline characteristics are presented according to the size of the ring (Table 1). Before surgical referral, all the patients had been treated with optimized medical regimens by his or her attending cardiologist, including angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, β-blockers, and diuretics.

Ethical committee approval was obtained from each institution, and individual consent was waived for this retrospective analysis. Written informed consent for the procedure was obtained from each patient before surgery.

Echocardiography

Two-dimensional and Doppler transthoracic echocardiography examinations were performed before and 1 month after surgery. All echocardiographic studies were done using commercially available 3.75-MHz transducers (Toshiba, Tokyo, Japan, and Hewlett-Packard Sonos) by expert echocardiographic examiners who were blinded to the clinical status of the patients and their operative data. Echocardiographic measurements included LV end-diastolic and end-systolic dimensions, LA dimension, LV ejection fraction, and right ventricular (RV) end-diastolic dimension. Postoperative transmitral mean gradient were measured by Doppler echocardiography. The mitral valve EOA was determined by the pressure half-time method[11] and indexed for BSA. The severity of regurgitation was classified as none (0), trivial (1+), mild (2+), moderate (3+), or severe (4+) in the present study.

Doppler-Derived Pulmonary Artery Pressure

Systolic pulmonary artery pressure (PAP) was calculated by adding the systolic pressure gradient across the tricuspid valve derived from tricuspid regurgitation, to the estimated right atrial pressure value.[12,13]

Table 1. Patient Characteristics

Variables	Physio 24 mm (n=66)	Physio 26 mm (n=42)
Age, y	67±9	63±9
Males	47 (71%)	39 (93%)
Body surface area, m^2	1.61±0.19	1.70±0.17*
New York Heart Association class		
I	0 (0%)	0 (0%)
II	2 (3%)	3 (7%)
III	54 (81%)	24 (57%)
IV	10 (15%)	15 (36%)
Echocardiographic data		
LV end-diastolic dimension, mm	64±6	70±9*
LV end-systolic dimension, mm	54±7	60±11*
LV ejection fraction, %	29±8	29±8
Left atrial dimension, mm	46±7	50±9
RV end-diastolic dimension, mm	33±7	33±5
Systolic PAP, mm Hg	46±14	47±13
Mitral regurgitation, 0/1+/2+/3+/4+	0/0/0/38/28	0/0/0/17/25
Tricuspid regurgitation, 0/1+/2+/3+/4+	2/22/17/16/9	2/7/21/11/1
ECG		
Left bundle-branch block	14 (21%)	9 (21%)
QRS duration >130 ms	13 (20%)	11 (26%)
History of cardiac resynchronization therapy	2 (3%)	5 (12%)
DDD pacemaker	1 (2%)	0 (0%)
Comorbidity		
Hypertension	39 (59%)	19 (45%)
Diabetes	36 (55%)	17 (40%)
Hyperlipidemia	28 (42%)	12 (29%)
Chronic obstructive lung disease	4 (6%)	4 (10%)
Chronic renal failure	27 (41%)	16 (38%)
Peripheral vascular disease	10 (15%)	3 (7%)
Cerebral vascular accident	14 (21%)	6 (14%)
Atrial fibrillation	24 (36%)	14 (33%)
History of ventricular arrhythmia	7 (11%)	12 (29%)
Previous cardiac surgery	6 (9%)	1 (2%)
Etiology of cardiomyopathy		
Idiopathic	22 (33%)	20 (48%)
Ischemic	44 (67%)	22 (52%)
Medications		
β-Blockers	43 (65%)	24 (57%)
ACE inhibitors	17 (26%)	6 (14%)
Angiotensin II receptor blockers	25 (38%)	8 (19%)
Long-acting nitrates	11 (17%)	8 (19%)
Diuretics	48 (73%)	26 (62%)
Operative data		
Cardiopulmonary bypass time, min	181±62	189±63
Aortic cross-clamp time, min	97±44	110±45
Concomitant procedures		
Coronary artery bypass grafting	27 (41%)	19 (45%)
Tricuspid annuloplasty	47 (71%)	21 (50%)
Modified maze procedure	16 (24%)	13 (31%)
Pulmonary vein isolation	8 (12%)	1 (2%)

LV indicates left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; ACE, angiotensin converting enzyme; and NS, not significant ($P>0.05$).

*$P<0.05$ versus Physio 24-mm.

Cardiac Catheterization

Right and left heart catheterization procedures were performed, using standard techniques before and 1 month (within 1 day of echocardiography) after surgery. The purposes of the cardiac catheterization and the invasive nature of the procedure were explained in detail to all patients, and only those who gave informed consent underwent catheterizations. The indications for postoperative catheterization were not selective. None had complications at the preoperative or postoperative catheterization. As a result, preoperative coronary arteriography was performed for all 108 patients, but left ventriculography and hemodynamic measurements were performed for 97 (90%) and 75 (69%), respectively. After surgery, 89 of the 108 patients (82%) underwent left ventriculography and 58 (54%) underwent hemodynamic measurements.

Before left ventriculography, standard pressure measurements were obtained to evaluate the LV systolic pressure, LV end-diastolic pressure (LVEDP), pulmonary capillary wedge pressure (PCWP); systolic, diastolic, and mean PAP; RV systolic pressure, RVEDP, and right atrial pressure. Right-sided pressures were obtained using a Swan-Ganz catheter. Cardiac output was determined with the thermodilution method. In addition, the systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were also calculated.

Hemodynamic Assessment of Mitral Valve Performance

The gradient across the mitral valve was calculated as the pressure difference between mean PCWP and LVEDP, although it is better to determine transmitral gradients using simultaneous recordings.

Classification of the Severity of MS, Prosthesis-Patient Mismatch, and PH

MS severity was categorized classically as mild (EOA >1.5 cm^2, mean gradient <5 mm Hg), moderate (EOA 1.0 to 1.5 cm^2, mean gradient 5 to 10 mm Hg), or severe (EOA <1.0 cm^2, mean gradient >10 mm Hg).

Indeed, there is no single parameter that defines the severity of functional MS that is possibly induced by an RMA procedure. In the present study, functional MS severity was categorized according to the level of the in vivo EOA in relation to patient body size; PPM was defined as mild and not clinically significant if the indexed EOA was >1.2 cm^2/m^2, as moderate if it was >0.9 to 1.2 cm^2/m^2, and as severe if it was ≤ 0.9 cm^2/m^2.[8]

The severity of PH was also categorized as mild (systolic PAP <40 mm Hg), moderate (systolic PAP 40 to 60 mm Hg), or severe (systolic PAP >60 mm Hg).

Surgical Procedures

A median sternotomy was performed under a mild hypothermic cardiopulmonary bypass with intermittent cold blood cardioplegia. A stringent restrictive (2 to 3 sizes smaller than measured) mitral annuloplasty was performed for all patients. The ring size was selected according to the surgeon's preference (Ka.T., T. M., and Y.S.) at each hospital, considering the patient's body size. Sixty-six (61%) patients received a 24-mm Physio ring (geometric orifice area, 2.74 cm^2) and 42 (39%) a 26-mm Physio ring (geometric orifice area, 3.25 cm^2). Data regarding the geometric orifice area of the ring were supplied by the manufacturer. All relevant surgical data are summarized in Table 1.

Clinical Follow-Up

Clinical follow-up examinations were completed for all 108 patients (100%), with a mean duration of 33 ± 18 months. Every 6 months to 1 year, each patient was assessed in the department as well as by his or her primary cardiologist. A retrospective review of the medical records of these patients was performed to obtain the preoperative and postoperative data. Current information was obtained by calling the patient or the referring cardiologist. We also reviewed the postoperative adverse cardiac events defined as late cardiac-related death, myocardial infarction, thromboembolism, readmission for heart failure, and ventricular arrhythmia requiring implantation of an intracardiac defibrillator.

Statistical Analysis

Continuous variables are summarized as mean$\pm$SD and categorical variables as frequencies and proportions. All the continuous variables were checked for normality using the Shapiro-Wilk test and normal probability plot. Normally distributed variables were compared using the Student t test and nonnormally distributed variables were compared with the Mann-Whitney U test. Categorical variables were compared using the χ^2 analysis or Fisher exact test, as appropriate. Preoperative and postoperative hemodynamic variables were assessed by repeated-measures ANOVA with group, time, and group-time interaction effects. Nonnormally distributed variables tested in the repeated ANOVA were natural log-transformed to satisfy normality of the used models, as appropriate. Correlation between nonnormally distributed variables were tested with Spearman correlation coefficient (ρ).

Stepwise multiple linear regression analyses were performed to identify the determinants of Doppler-derived or catheter-measured systolic PAP. The Doppler-derived systolic PAP and catheter-measured systolic PAP were natural log-transformed to satisfy normality of the used models. Factors obtaining a probability value less than 0.1 in the univariate analysis, based on Spearman correlation coefficient were then entered appropriately into the stepwise multiple linear regression model. Regression diagnostics was used to assess the obtained models for collinearity and residual nonnormality and heteroscedasticity. The results are summarized as correlation coefficients (ρ) and standardized partial regression coefficients (SPRCs).

Univariate and multivariate analyses of the predictors for adverse cardiac time to events were performed using Cox proportional hazards models. Factors obtaining a probability value less than 0.1 in the univariate Cox proportional hazards analysis were then entered appropriately into the multivariate fashion, using stepwise variable selection. The results are summarized as hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical significance was defined as a probability value <0.05. Statistical analyses were performed using JMP 7.0 (SAS Institute, Cary, NC) and SPSS software (version 17.0, SPSS Inc).

Results

Postoperative Echocardiographic Data

After surgery, none of the patients showed a significant ($>2+$) level of residual MR (Table 2). The pressure half-time was 92 ± 14 ms in all the patients (range, 67 to 129 ms versus normal value, 40 to 60 ms), which was prolonged and suggested the presence of gradients across the mitral valve. The transmitral mean gradient value was 2.9 ± 1.1 mm Hg (range, 1.1 to 6.2 mm Hg). Ninety-eight of the 108 patients (91%; 95% CI, 84% to 95%) had a transmitral mean gradient value <5 mm Hg (mild MS), whereas 10 (9%; 95% CI, 5% to 16%) had a mean gradient value ≥ 5 mm Hg (moderate MS). The mitral valve EOA value was 2.4 ± 0.4 cm^2 (range, 1.7 to 3.3 cm^2), and none of the patients had a value <1.5 cm^2. The indexed EOA value was 1.51 ± 0.32 cm^2/m^2 (range, 0.84 to 2.46 cm^2/m^2). Twenty-one (19%; 95% CI, 13% to 28%) showed moderate PPM (an indexed EOA >0.9 to ≤ 1.2 cm^2/m^2), and 2 (2%; 95% CI, 0.5 to 6.5%) had severe PPM (an indexed EOA ≤ 0.9 cm^2/m^2). The mean value for systolic PAP was 32 ± 8 mm Hg (range, 18 to 53 mm Hg). Seventeen patients (16%; 95% CI, 11% to 26%) showed moderate PH (systolic PAP, 40 to 60 mm Hg), and none had severe PH (systolic PAP >60 mm Hg) after surgery. Notably, patients with a 24-mm ring

Table 2. Postoperative Echocardiographic Measurements

Variables	All Cases (n=108)	Physio 24 mm (n=66)	Physio 26 mm (n=42)	*P* Value*
Geometric orifice area, cm^2		2.74	3.25	
Indexed GOA, cm^2/m^2	1.80±0.22	1.72±0.20	1.93±0.19	<0.001
Pressure half-time, ms	92±14	96±15	86±11	<0.001
Mitral mean gradient, mm Hg	2.9±1.1	3.1±1.1	2.6±1.1	0.01
<5 mm Hg	98 (91%)	58 (88%)	40 (95%)	NS
≥5 mm Hg	10 (9%)	8 (12%)	2 (5%)	
Mitral valve EOA, cm^2	2.4±0.4	2.3±0.4	2.6±0.3	<0.001
≥1.5 cm^2	108 (100%)	66 (100%)	42 (100%)	NS
<1.5 cm^2	0 (0%)	0 (0%)	0 (0%)	
Mitral valve EOA/GOA	0.83±0.12	0.86±0.13	0.80±0.10	0.01
Indexed EOA, cm^2/m^2	1.51±0.32	1.48±0.34	1.54±0.27	NS
>1.2 cm^2/m^2	85 (79%)	48 (73%)	37 (88%)	NS
>0.9 to 1.2 cm^2/m^2	21 (19%)	17 (26%)	4 (10%)	
≤0.9 cm^2/m^2	2 (2%)	1 (1%)	1 (2%)	
Indexed EOA/GOA, $/m^2$	0.52±0.11	0.54±0.12	0.48±0.08	0.003
Systolic PAP, mm Hg	32±8	31±9‡	32±6‡	NS
Not determined†	9 (8%)	5 (8%)	4 (10%)	NS
<40 mm Hg	82 (76%)	51 (77%)	31 (74%)	
40–60 mm Hg	17 (16%)	10 (15%)	7 (17%)	
>60 mm Hg	0 (0%)	0 (0%)	0 (0%)	
LV end-diastolic dimension, mm	61±9	59±7‡	64±10‡	NS
LV end-systolic dimension, mm	52±11	50±9‡	55±12‡	0.04
LV ejection fraction, %	33±10	34±10‡	32±10‡	NS
Left atrial dimension, mm	43±7	42±6‡	45±8‡	NS
RV end-diastolic dimension, mm	29±6	30±6‡	27±6‡	NS
Residual mitral regurgitation, 0/1+/2+/3+/4+	66/34/8/0/0	40/22/4/0/0	26/12/4/0/0	NS
Residual tricuspid regurgitation, 0/1+/2+/3+/4+	9/86/13/0/0	5/56/5/0/0	4/30/8/0/0	NS

GOA indicates geometric orifice area; EOA, effective orifice area; PAP, pulmonary artery pressure; LV, left ventricular; and RV, right ventricular.

*Physio 24-mm versus Physio 26-mm.

†Data were not available due to absence of tricuspid regurgitation.

‡$P<0.05$ versus variables at baseline in each group.

had a greater mean transmitral gradient, smaller mitral valve EOA, and longer pressure half-time compared with those with a 26-mm ring, whereas there was no difference between the groups with regard to the indexed EOA and systolic PAP. In general, the transmitral mean gradient correlated inversely with the indexed EOA value ($\rho=-0.30$ $P=0.002$), and correlated positively with the BSA ($\rho=0.27$, $P=0.006$).

Other LV dimension and function variables substantially improved in both groups.

Determinants of Postoperative Doppler-Derived Systolic PAP 1 Month After RMA

Postoperative Doppler-derived systolic PAP correlated with the Doppler-derived transmitral mean gradient ($\rho=0.23$, $P=0.02$) but did not correlate with the EOA or indexed EOA(Table 3). Postoperative systolic PAP also correlated with the catheter-derived postoperative PCWP ($\rho=0.40$, $P=0.002$), LVEDP ($\rho=0.38$, $P=0.004$), and PVR ($\rho=0.66$, $P<0.001$). Multivariate analysis showed that PVR had the most important contribution (SPRC=0.62), followed by LVEDP (SPRC=0.28), whereas the transmitral gradient had a minimal contribution (SPRC=0.24). Postoperative PCWP was not entered into the multivariate analysis because of a strong correlation between PCWP and LVEDP ($\rho=0.87$). Regression diagnostics showed no evidence of collinearity and residual nonnormality and heteroscedasticity in the obtained models.

Preoperative and Postoperative Hemodynamic Data

From baseline to 1 month after surgery, LV volumes decreased and ejection fraction improved in both patient groups (Table 4). LV systolic pressure did not change, whereas LVEDP, PCWP, systolic, and mean PAP decreased significantly. Other hemodynamic parameters such as cardiac index, PVR, and SVR also improved significantly or showed a trend toward normal in both groups. Importantly, there were no differences in postoperative LV function or hemodynamic parameters between the 2 groups, which received different sized rings.

Table 3. Determinants of Postoperative Doppler-Derived Systolic PAP 1 Month After RMA

	Univariate		Multivariate	
Variables	ρ	*P* Value	SPRC	*P* Value
Preop echocardiographic parameters (n=108)				
LVEDD, mm		NS		
LVESD, mm		NS		
LV ejection fraction, %		NS		
LA dimension, mm	0.22	0.03		
RVEDD, mm		NS		
Systolic PAP, mm Hg	0.35	<0.001		
Preop volume and function parameters (n=97)				
LVEDVI, mL/m^2		NS		
LVESVI, mL/m^2		NS		
LV ejection fraction, %		NS		
Preop hemodynamic parameters (n=75)				
LVSP, mm Hg		NS		
LVEDP, mm Hg	0.21	0.08		
PCWP, mm Hg	0.21	0.08		
Systolic PAP, mm Hg	0.21	0.08		
Cardiac index, L/min/m^2	−0.28	0.009		
PVR, dyne · s · cm^{-5}	0.63	<0.001		
SVR, dyne · s · cm^{-5}	0.26	0.02		
Postop echocardiographic parameters (n=108)				
LVEDD, mm		NS		
LVESD, mm		NS		
LV ejection fraction, %		NS		
LA dimension, mm	0.18	0.07		
RVEDD, mm		NS		
Mitral valve EOA, cm^2		NS		
Indexed EOA, cm^2/m^2		NS		
Pressure half-time, ms		NS		
Mitral mean gradient, mm Hg	0.23	0.02	0.24	0.01
Postop volume and function parameters (n=89)				
LVEDVI, mL/m^2		NS		
LVESVI, mL/m^2	0.25	0.02		
LV ejection fraction, %	−0.26	0.02		
Postop hemodynamic parameters (n=58)*				
LVSP, mm Hg		NS		
LVEDP, mm Hg	0.38	0.004	0.28	0.01
PCWP, mm Hg†	0.40	0.002		
Mitral gradient (mean PCWP-LVEDP), mm Hg		NS		
Cardiac index, L/min/m^2		NS		
PVR, dyne · s · cm^{-5}	0.66	<0.001	0.62	<0.001
SVR, dyne · s · cm^{-5}		NS		

SPRC indicates standardized partial regression coefficient; LV, left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; EOA, effective orifice area; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LA, left atrial; RVEDD, right ventricular end-diastolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVSP, left ventricular systolic pressure; and NS, not significant ($P>0.05$).

*Postoperative catheter-measured systolic PAP was not tested in this analysis.

†Postoperative PCWP was not entered into the multivariate analysis because of a strong correlation between PCWP and LVEDP ($\rho=0.87$).

The postoperative transmitral pressure gradient value, calculated as the pressure difference between mean PCWP and LVEDP, was 3.0±1.2 mm Hg (range, 1 to 7 mm Hg). The mean value for catheter-measured postoperative systolic PAP was 33±8 mm Hg (range, 18 to 54 mm Hg). Fifteen of the 58 patients (26%; 95% CI, 16% to 38%) showed moderate PH (systolic PAP, 40 to 60 mm Hg), and none had severe PH (systolic PAP, >60 mm Hg) after surgery. Notably, patients with a 24-mm ring had greater transmitral pressure gradients compared with patients with a 26-mm ring, whereas there was no difference in systolic PAP between the groups. There were also no differences for the other hemodynamic measurements.

In general, the transmitral pressure gradient correlated positively with cardiac output ($\rho=0.77$, $P<0.001$) and heart rate ($\rho=0.27$, $P=0.05$).

Determinants of Postoperative Catheter-Measured Systolic PAP 1 Month After RMA

In univariate analyses, the postoperative catheter-measured systolic PAP correlated with the PCWP ($\rho=0.70$, $P<0.001$), LVEDP ($\rho=0.56$, $P<0.001$), transmitral pressure gradient ($\rho=0.52$, $P<0.001$), cardiac index ($\rho=0.28$, $P=0.04$), and PVR ($\rho=0.54$, $P<0.001$) (Table 5). Multivariate analysis showed that LVEDP had the most important contribution (SPRC=0.51), followed by PVR (SPRC=0.47) and the cardiac index (SPRC=0.37), whereas the transmitral pressure gradient had a minimal contribution (SPRC=0.20). Postoperative PCWP was not entered into the multivariate analysis because of a strong correlation between PCWP and LVEDP ($\rho=0.87$). Regression diagnostics showed no evidence of collinearity, and residual nonnormality and heteroscedasticity in the obtained models.

Correlation Between Invasive Hemodynamic Measurements and Noninvasive Doppler-Derived Variables

Spearman correlation analysis showed a strong correlation ($\rho=0.94$, $P<0.001$) between the catheter-measured mitral pressure gradient and Doppler-derived transmitral mean gradient values. There was also a substantial correlation

Table 4. Preoperative and Postoperative Hemodynamic Measurements

	Physio No. 24 (n=32)		Physio No. 26 (n=26)				
Variables	Preop	Postop	Preop	Postop	Group	Time	Group-Time
LV end-diastolic volume index, mL/m^2	135±35	109±35	150±47	126±49	NS	<0.001	NS
LV end-systolic volume index, mL/m^2	101±30	78±33	113±44	90±48	NS	<0.001	NS
LV ejection fraction, %	26±7	30±12	26±8	31±12	NS	0.002	NS
LV systolic pressure, mm Hg	115±21	121±14	123±21	124±24	NS	NS	NS
LVEDP, mm Hg	17±6	9±3	17±7	11±3	NS	<0.001	NS
PCWP, mm Hg	21±6	13±3	21±8	13±3	NS	<0.001	NS
Mitral gradient (=mean PCWP−LVEDP), mm Hg		3.3±1.4		2.6±1.0*			
Systolic PAP, mm Hg	46±13	34±9	46±16	34±9	NS	<0.001	NS
<40 mm Hg	10 (31%)	24 (75%)	11 (42%)	19 (73%)			
40–60 mm Hg	19 (60%)	8 (25%)	10 (38%)	7 (27%)			
>60 mm Hg	3 (9%)	0 (0%)	5 (19%)	0 (0%)			
Mean PAP, mm Hg	32±7	21±6	33±9	22±6	NS	<0.001	NS
Right atrial pressure, mm Hg	8±4	8±3	7±4	8±2	NS	NS	NS
Heart rate, beats/min	78±11	79±13	76±15	81±10	NS	NS	NS
Cardiac index, L/min/m^2	2.7±0.7	2.9±0.7	2.3±0.6	2.8±0.6	NS	<0.001	0.02
Stroke volume index, mL/m^2	36±11	38±10	31±9	35±5	NS	0.02	NS
PVR, dyne·s·cm^{-5}	235±73	150±75	250±71	156±67	NS	<0.001	NS
SVR, dyne·s·cm^{-5}	1470±460	1370±440	1620±400	1220±250	NS	<0.001	0.02

LV indicates left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; EDP, end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; EOA, effective orifice area; and NS, not significant ($P>0.05$).

*$P<0.05$ versus Physio 24-mm.

($\rho=0.67$, $P<0.001$) between the catheter-measured systolic PAP and Doppler-derived systolic PAP values.

Clinical Outcomes

In this series, the actuarial survival rates at 1, 2, and 3 years after surgery were 95±2%, 92±3%, and 87±4%, respectively. During the follow-up period, there were 6 late cardiac-related deaths, 29 late readmissions due to heart failure, 1 myocardial infarction, and 4 ventricular arrhythmias. Freedom from adverse cardiac events at 1, 2, and 3 years after surgery was 88±3%, 78±4%, and 68±5%, respectively. There was no difference in freedom from adverse cardiac events between patients with an indexed EOA of >1.2 cm^2/m^2 versus ≤1.2 cm^2/m^2.

Among the preoperative variables investigated, preoperative PAP >60 mm Hg (HR, 4.5; 95% CI, 2.2 to 8.9) and a history of ventricular arrhythmia (HR 2.1, 95% CI: 1.0 to 4.6) were the predictors of the postoperative adverse cardiac events (Table 6). Furthermore, among the postoperative echocardiographic variables and surgical data, a postoperative PAP >40 mm Hg (HR, 4.6; 95% CI, 2.3 to 9.3) and residual tricuspid regurgitation (HR, 2.5; 95% CI, 1.0 to 6.1) were the predictors of adverse cardiac events (Table 7).

Discussion

This study constitutes an initial report evaluating the association between iatrogenic functional MS, PPM in terms of in vivo indexed EOA, residual PH, and clinical outcome (late adverse cardiac events) after RMA in patients with advanced cardiomyopathy.

The present echocardiographic results are largely consistent with those presented in previous studies, especially in terms of the transmitral mean gradient, mitral valve area, and systolic PAP.[3,4,14–16] In contrast, Magne et al[5] reported a higher mean gradient (6±2 mm Hg), smaller mitral valve area (1.5±0.3 cm^2), and higher systolic PAP (42±13 mm Hg) values compared with other prior studies. Among the 24 patients in their study, 54% (n=13) had a mean gradient ≥5 mm Hg, 54% (n=13) had a valve area ≤1.5 cm^2, and 45% (n=11) had a systolic PAP ≥40 mm Hg. From those findings, they concluded that a large proportion (>50%) of the patients who underwent RMA had moderate functional MS and significant PH after the operation. In addition, a recent study[9] also reported a high prevalence (42%) of patients with a small valve area, ≤1.5 cm^2. However, in that study, the transmitral gradients were similar to those reported in many other studies.[3,4,14–16]

In the present study, only 9% of the patients showed a mean gradient ≥5 mm Hg, and none had a valve area ≤1.5 cm^2. The contrasting results with regard to valve area as compared to the study of Magne et al[5] can be explained by the different methods utilized for determining valve area. Magne et al[5] calculated mitral valve area using the continuity equation, whereas many other investigators, including our group, determined it using the pressure half-time method or direct planimetry.[3,4,14–16] In addition, the difference in results for the transmitral gradient may be due to subject selection bias or the patient's BSA. The mean BSA of their patients was greater than that of our patients (1.8±0.2 m^2 versus 1.65±0.19 m^2). Magne et al[5] also found a significant corre-

Table 5. Determinants of Postoperative Catheter-Measured Systolic PAP 1 Month After RMA

	Univariate		Multivariate	
Variables	ρ	*P* Value	SPRC	*P* Value
Preop echocardiographic parameters (n=108)				
LVEDD, mm		NS		
LVESD, mm		NS		
LV ejection fraction, %		NS		
LA dimension, mm	0.35	0.007	0.23	0.009
RVEDD, mm		NS		
Systolic PAP, mm Hg	0.54	<0.001		
Preop volume and function parameters (n=97)				
LVEDVI, mL/m^2		NS		
LVESVI, mL/m^2		NS		
LV ejection fraction, %		NS		
Preop hemodynamic parameters (n=75)				
LVSP, mm Hg		NS		
LVEDP, mm Hg	0.26	0.08		
PCWP, mm Hg	0.28	0.06		
Systolic PAP, mm Hg	0.33	0.02		
Cardiac index, L/min/m^2		NS		
PVR, dyne · s · cm^{-5}	0.28	0.04		
SVR, dyne · s · cm^{-5}		NS		
Postop echocardiographic parameters (n=108)*				
LVEDD, mm		NS		
LVESD, mm		NS		
LV ejection fraction, %		NS		
LA dimension, mm	0.42	0.001		
RVEDD, mm		NS		
Mitral valve EOA, cm^2		NS		
Indexed EOA, cm^2/m^2		NS		
Pressure half-time, ms		NS		
Mitral mean gradient, mm Hg	0.52	<0.001	0.20	0.006
Postop volume and function parameters (n=89)				
LVEDVI, mL/m^2		NS		
LVESVI, mL/m^2		NS		
LV ejection fraction, %		NS		
Postop hemodynamic parameters (n=58)				
LVSP, mm Hg		NS		
LVEDP, mm Hg	0.56	<0.001	0.51	<0.001
PCWP, mm Hg†	0.70	<0.001		
Mitral gradient (mean PCWP−LVEDP), mm Hg	0.44	<0.001		
Cardiac index, L/min/m^2	0.28	0.04	0.37	<0.001
PVR, dyne · s · cm^{-5}	0.54	<0.001	0.47	<0.001
SVR, dyne · s · cm^{-5}		NS		

LV indicates left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; EOA, effective orifice area; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LA, left atrial; RVEDD, right ventricular end-diastolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVSP, left ventricular systolic pressure; and NS, not significant ($P>0.05$).

*Postoperative Doppler-derived systolic PAP was not tested in this analysis.

†Postoperative PCWP was not entered into the multivariate analysis because of a strong correlation between PCWP and LVEDP ($\rho=0.87$).

lation between the mitral peak gradient and systolic PAP ($r=0.70$) and concluded that functional MS after RMA was strongly associated with postoperative elevated PAP and reduced exercise capacity. We found a weak but significant correlation between the mean mitral gradient and systolic PAP, which may support their speculation. However, it remains unknown whether the mitral gradient is the sole factor that affects postoperative elevated PAP.

There have been few hemodynamic studies on possible functional MS after RMA. Our hemodynamic results provide additional information about the gradients across the mitral valve and possible factors relating to postoperative PH. The present study also found a small but significant transmitral pressure gradient, calculated as the pressure difference between mean PCWP and LVEDP, which ranged from 1 to 7 mm Hg. The actual value may be slightly smaller than predicted by this pressure difference.[17] Nevertheless, about 10% of our patients (6 of 58) had a pressure gradient ≥5 mm Hg, suggesting the presence of hemodynamically substantial MS. Interestingly, in the present study, we found a strong correlation between the catheter-determined pressure gradient calculated from the mean PCWP and LVEDP, and the Doppler-derived mean gradient. This close correlation allowed us to predict the actual transmitral mean gradient, based on the pressure difference at end-diastole and to analyze relevant factors related to postoperative PH.

Hemodynamic Determinants of Postoperative PAP

Our multivariate analysis using hemodynamic variables showed that the most important determinant of systolic PAP was LVEDP, followed by PVR, and then cardiac index, whereas the contribution of the transmitral pressure gradient was the lowest of the parameters investigated. These findings suggest that the main mechanism of postoperative PH may be high LVEDP, probably due to LV systolic and diastolic dysfunction, whereas another may be pulmonary vascular disease secondary to a preoperative pulmonary hypertensive state. The contribution of a transmitral pressure gradient created by the use of an undersized ring to postoperative PH seemed relatively small in our patients.

Table 6. Preoperative Parameters Associating With Adverse Cardiac Events

	Univariate		Multivariate	
Variables	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)
Clinical variables (n=108)				
Age, y	NS			
Ischemic etiology	NS			
Female	NS			
Duration of heart failure, mo	<0.001	1.01 (1.01–1.02)		
Hypertension	NS			
Diabetes	0.09	1.8 (0.9–3.6)		
Hyperlipidemia	NS			
Chronic renal failure	NS			
Peripheral vascular disease	NS			
Cerebral vascular accident	NS			
Atrial fibrillation	NS			
History of ventricular arrhythmia	0.03	2.3 (1.1–4.9)	0.04	2.1 (1.0–4.6)
Chronic obstructive pulmonary disease	NS			
Previous cardiac surgery	NS			
Preop echocardiographic parameters (n=108)				
LV end-diastolic dimension, mm	NS			
LV end-diastolic dimension >65 mm	NS			
LV end-systolic dimension, mm	0.02	1.05 (1.01–1.08)		
LV end-systolic dimension >50 mm	NS			
LV ejection fraction, %	0.006	0.94 (0.90–0.98)		
LV ejection fraction <25%	0.03	2.2 (1.1–4.3)		
Left atrial dimension, mm	NS			
RV end-diastolic dimension, mm	NS			
Systolic PAP, mm Hg*	0.04	1.02 (1.00–1.05)		
Systolic PAP >60 mm Hg	<0.001	4.6 (2.3–9.1)	<0.001	4.5 (2.2–8.9)
Preop volume and function parameters (n=97)				
LV end-diastolic volume index, mL/m^2	NS			
LV end-diastolic volume index >120 mL/m^2	NS			
LV end-systolic volume index, mL/m^2	NS			
LV end-systolic volume index >90 mL/m^2	NS			
LV ejection fraction, %	NS			
LV ejection fraction <25%	NS			
Preop hemodynamic parameters (n=75)				
LV systolic pressure, mm Hg	NS			
LVEDP, mm Hg	NS			
PCWP, mm Hg	NS			
Systolic PAP, mm Hg	NS			
Mean PAP, mm Hg	NS			
Cardiac index, L/min/m^2	0.07	0.6 (0.3–1.1)		
PVR, dyne · s · cm^{-5}	0.002	1.008 (1.00–1.01)		
PVR index, dyne · s · cm^{-5} · m^2	0.004	1.004 (1.001–1.007)		
SVR, dyne · s · cm^{-5}	0.08	1.001 (1.000–1.002)		
SVR index, dyne · s · cm^{-5} · m^2	NS			

CI indicates confidence interval; LV, left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; EDP, end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; and NS, not significant (P>0.05).

*Systolic PAP (continuous variable) was not entered into the multivariate analysis.

Table 7. Postoperative Parameters Associating With Adverse Cardiac Events

	Univariate		Multivariate	
Variables	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)
Postop echocardiographic parameters (n=108)				
LV end-diastolic dimension, mm	0.03	1.04 (1.00–1.08)		
LV end-systolic dimension, mm	0.005	1.05 (1.01–1.08)		
LV ejection fraction, %	0.001	0.94 (0.91–0.98)		
Left atrial dimension, mm	NS			
RV end-diastolic dimension, mm	NS			
Systolic PAP, mm Hg*	<0.001	1.1 (1.04–1.13)		
Systolic PAP >40 mm Hg	<0.001	5.2 (2.6–10)	<0.001	4.6 (2.3–9.3)
Mitral valve EOA, cm^2	NS			
Indexed EOA, cm^2/m^2	NS			
Indexed EOA ≤1.2 cm^2/m^2	0.09	0.53 (0.26–1.09)		
Pressure half-time, ms	0.07	1.02 (0.99–1.04)		
Mitral mean gradient, mm Hg	0.03	1.36 (1.04–1.78)		
Mitral mean gradient ≥5 mm Hg	NS			
Residual mitral regurgitation†	NS			
Residual tricuspid regurgitation†	0.004	3.55 (1.5–8.4)	0.04	2.5 (1.0–6.1)
Surgical data (n=108)				
Ring size	NS			
Concomitant coronary artery bypass grafting	0.02	0.4 (0.2–0.8)		
Concomitant tricuspid annuloplasty	NS			
Concomitant maze procedure	NS			

CI indicates confidence interval; LV indicates left ventricular; RV, right ventricular; PAP, pulmonary artery pressure; EOA, effective orifice area; and NS, not significant ($P>0.05$).

*Systolic PAP was not entered into the multivariate analysis.

†Greater than or equal to mild grade.

Impact of the RMA Procedure on Hemodynamic and Clinical Results

The present patients with a 24-mm ring had a smaller mitral valve area and slightly greater transmitral mean gradient in echocardiographic findings, as well as a greater valve gradient in the hemodynamic evaluation, compared with those with a 26-mm ring. Despite these differences in mitral valve performance, there were no differences between the 2 groups in regard to postoperative LV volume and systolic function, PAPs, or the other measured hemodynamic parameters. Thus, in our patients, who had a lower BSA compared with those in previous studies, the use of a small prosthetic ring (24-mm Physio ring) did not appear to have a negative influence on the postoperative hemodynamic state over the short term.

Given that the normal mitral valve area is 4.0 to 5.0 cm^2, the 24- and 26-mm rings have obviously smaller orifice areas and are at least mildly obstructive to the antegrade mitral flow. The severity of this PPM can be categorized as mild, moderate, or severe according to the "in vivo" EOA indexed for the patient's BSA, as in previous studies.[7,8] Several studies have demonstrated that after mitral valve replacement, moderate PPM (indexed EOA ≤1.2 cm^2/m^2) is not uncommon, and that it has negative impacts on postoperative residual PH and late mortality and morbidity.[7,8,18] Other authors have suggested that moderate PPM in these patients is of less importance.[19,20]

In contrast, the prevalence and prognostic impact of PPM after RMA has not been well established. Our data showed that, following RMA, a considerable proportion (>20%) of patients had PPM, defined as an indexed EOA ≤1.2 cm^2/m^2. This mismatch occurred in 27% of the patients with a 24-mm ring and 12% with a 26-mm ring, which was not statistically different. Given that the pressure half-time method may overestimate the actual valve orifice area by about 10%, our in vivo EOA values suggest that the size 24- and 26-mm prosthetic rings may be too small, respectively, for patients with a BSA >1.75 to 1.80 m^2 or >1.90 to 2.00 m^2. However, it remains unclear whether such a mismatch after RMA has a negative impact on patient's prognosis.

In the present study, preoperative and postoperative residual PH, due to LV dysfunction and secondary pulmonary vascular disease, was more strongly associated with adverse cardiac events after RMA than was the severity of functional MS or the level of PPM. A Doppler-derived mean gradient of ≥5 mm Hg or an indexed EOA of ≤1.2 cm^2/m^2 did not predict adverse cardiac events during our short-term follow-up. We speculate that our identification of a negative prognostic role (a higher risk of adverse cardiac events) of this iatrogenic MS would have been masked in our analysis by the more important risk factors.

Study Limitations

The main limitation of this study is its retrospective design, as hemodynamic data could not be obtained from all of the patients, which may have resulted in a bias and restrict the statistical power of the findings. Also, in fully describing these data we have performed a large number of statistical tests, inflating the probability of making one or more type I errors across all the analyses presented. Therefore, our results should be interpreted cautiously until verified in an independent, prospective study. Furthermore, simultaneous LA and LV pressure tracings were not available, and therefore the actual mean transmitral pressure gradients and mitral valve EOA could not be determined using the Gorlin formula. In our echocardiographic and hemodynamic evaluations, the parameters were measured only in a resting condition; a dynamic exercise test with a bicycle ergometer, dobutamine stress test, or 6-minute walk test was not performed. However, data obtained from those stress tests would not have changed our conclusion. Finally, we only investigated patients who received a 24- or 26-mm Physio ring. Therefore, the results may not be applicable to patients who receive a different size or type of ring.

Conclusion

In the present study, the RMA procedure led to varying degrees of mitral valve obstruction in terms of higher transmitral mean pressure gradients (about 9% of patients) and a lesser EOA, as indexed for each patient's BSA (>20% of patients). This hemodynamic sequel was weakly associated with postoperative residual PH. However, postoperative elevated PAP was strongly associated with an elevated LVEDP and increased PVR. PH caused by LV dysfunction and pulmonary vascular disease was the most important predictor for outcomes in this study. The prognostic impact of iatrogenic MS after RMA would be hard to detect because of masking by more important risk factors.

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Disclosures

None.

References

1. Bolling SF, Deeb GM, Brunsting LA, Bach DS. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. *J Thorac Cardiovasc Surg*. 1995;109:676–683.
2. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg*. 1998;115:381–388.
3. Bax JJ, Braun J, Somer ST, Klautz R, Holman ER, Versteegh MI, Boersma E, Schalij MJ, van der Wall EE, Dion RA. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation*. 2004; 110(Suppl II):II-103–II-108.
4. Braun J, van de Veire NR, Klautz RJM, Versteegh MIM, Holman ER, Westenberg JJ, Boersma E, van der Wall EE, Bax JJ, Dion RA. Restrictive mitral annuloplasty cures ischemic mitral regurgitation and heart failure. *Ann Thorac Surg*. 2008;85:430–437.
5. Magne J, Sénéchal M, Mathieu P, Dumesnil JG, Dagenais F, Pibarot P. Restrictive annuloplasty for ischemic mitral regurgitation may induce functional mitral stenosis. *J Am Coll Cardiol*. 2008;51:1692–1701.
6. Dumesnil JG, Yoganathan AP. Valve prosthesis hemodynamics and the problem of high transprosthetic pressure gradients. *Eur J Cardiothorac Surg*. 1992;6(Suppl 1):S34–S37.
7. Li M, Dumesnil JG, Mathieu P, Pibarot P. Impact of valve prosthesis-patient mismatch on pulmonary arterial pressure after mitral valve replacement. *J Am Coll Cardiol*. 2005;45:1034–1040.
8. Magne J, Mathieu P, Dumesnil JG, Tanné D, Dagenais F, Doyle D, Pibarot P. Impact of prosthesis-patient mismatch on survival after mitral valve replacement. *Circulation*. 2007;115:1417–1425.
9. Kubota K, Otsuji Y, Ueno T, Koriyama C, Levine RA, Sakata R, Tei C. Functional mitral stenosis after surgical annuloplasty for ischemic mitral regurgitation: importance of subvalvular tethering in the mechanism and dynamic deterioration during exertion. *J Thorac Cardiovasc Surg*. 2010;140:617–623.
10. Williams ML, Daneshmand MA, Jollis JG, Horton JR, Shaw LK, Swaminathan M, Davis RD, Glower DD, Smith PK, Milano CA. Mitral gradients and frequency of recurrence of mitral regurgitation after ring annuloplasty for ischemic mitral regurgitation. *Ann Thorac Surg*. 2009;88:1197–1201.
11. Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. *Circulation*. 1979;60: 1096–1104.
12. Pepi M, Tamborini G, Galli C, Barbier P, Doria E, Berti M, Guazzi M, Fiorentini C. A new formula for echo-Doppler estimation of right ventricular systolic pressure. *J Am Soc Echocardiogr*. 1994;7:20–26.
13. Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am J Cardiol*. 1990;66:493–496.
14. De Bonis M, Lapenna E, Verzini A, La Canna G, Grimaldi A, Torracca L, Maisano F, Alfieri O. Recurrence of mitral regurgitation parallels the absence of left ventricular reverse remodeling after mitral repair in advanced dilated cardiomyopathy. *Ann Thorac Surg*. 2008;85:932–939.
15. Geidel S, Lass M, Schneider C, Groth G, Boczor S, Kuck KH, Ostermeyer J. Downsizing of the mitral valve and coronary revascularization in severe ischemic mitral regurgitation results in reverse left ventricular and left atrial remodeling. *Eur J Cardiothorac Surg*. 2005;27:1011–1016.
16. Gelsomino S, Lorusso R, Capecchi I, Rostagno C, Romagnoli S, Billè G, De Cicco G, Tetta C, Stefàno P, Gensini GF. Left ventricular reverse remodeling after undersized mitral ring annuloplasty in patients with ischemic regurgitation. *Ann Thorac Surg*. 2008;85:1319–1330.
17. Lange RA, Moore DM Jr, Cigarroa RG, Hillis LD. Use of pulmonary capillary wedge pressure to assess severity of mitral stenosis: is true left atrial pressure needed in this condition? *J Am Coll Cardiol*. 1989;13:825–831.
18. Lam BK, Chan V, Hendry P, Ruel M, Masters R, Bedard P, Goldstein B, Rubens F, Mesana T. The impact of patient-prosthesis mismatch on late outcomes after mitral valve replacement. *J Thorac Cardiovasc Surg*. 2007;133:1464–1473.
19. Jamieson WR, Ye J, Higgins J, Cheung A, Fradet GJ, Skarsgard P, Germann E, Chan F, Lichtenstein SV. Effect of prosthesis-patient mismatch on long-term survival with mitral valve replacement: assessment to 15 years. *Ann Thorac Surg*. 2010;89:51–58.
20. Totaro P, Argano V. Patient-prosthesis mismatch after mitral valve replacement: myth or reality? *J Thorac Cardiovasc Surg*. 2007;134:697–701.

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Restrictive Mitral Annuloplasty With or Without Surgical Ventricular Restoration in Ischemic Dilated Cardiomyopathy With Severe Mitral Regurgitation

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Background—We assessed changes in left ventricular (LV) volume and function and in regional myocardial wall stress in noninfarcted segments after restrictive mitral annuloplasty (RMA) with or without surgical ventricular restoration (SVR).

Methods and Results—Thirty-nine patients with ischemic cardiomyopathy (ejection fraction ≤0.35) and severe mitral regurgitation (≥3) were studied before and 2.8 months after surgery with cine-angiographic multidetector computed tomography (cine-MDCT). Eighteen underwent RMA alone (RMA group) and 21 underwent RMA and SVR (RMA+SVR group). In addition to measuring conventional parameters (LV end-diastolic volume index [LVEDVI], LV end-systolic volume index [LVESVI], and LV ejection fraction), we evaluated the regional circumferential end-systolic wall stress and mean circumferential fiber shortening in both the basal and mid-LV regions using 3-dimensional cine-MDCT images. LV end-diastolic and end-systolic volume indexes were significantly greater in the RMA+SVR group than in the RMA group preoperatively, but these values did not differ significantly postoperatively. LV end-diastolic and end-systolic volume indexes decreased significantly, by 21% and 27% after RMA and by 35% and 42% after RMA and SVR, and the percent reductions in LV end-diastolic and end-systolic volume indexes were significantly larger in the RMA+SVR group. Regional end-systolic wall stress decreased and circumferential fiber shortening increased significantly in the noninfarcted regions after RMA with or without SVR.

Conclusions—RMA plus SVR showed a potentially greater reduction of LV end-diastolic and end-systolic volume indexes than RMA alone. In selected patients with more advanced LV remodeling, concomitant SVR may favorably affect the LV reverse-remodeling process induced by RMA. (***Circulation.*** **2011;124[suppl 1]:S107–S114.)**

Key Words: tomography ■ cardiomyopathy ■ mitral regurgitation ■ left ventricular remodeling ■ stress

Progress in understanding the intrinsic ventricular architecture during postinfarction remodeling and the introduction of valuable modifications to classic left ventricular (LV) aneurysm repair have extended the indication for surgical ventricular restoration (SVR) to include more-dilated ventricles with akinetic as well as regional dysfunction.[1] Several studies have shown that SVR is effective and relatively safe, with a favorable 5-year outcome,[2,3] although whether SVR improves the effectiveness of coronary artery bypass grafting (CABG) is debated.[4,5] SVR is frequently combined with restrictive mitral annuloplasty (RMA), and the impact of the combined procedure in patients with heart failure has been the subject of several recent studies. The role of concomitant SVR at the time of RMA is still controversial, and no clear guidelines exist.[6] The acute hemodynamic improvement induced by SVR may depend on a complex interplay of changes in LV geometry and LV wall stress.[7,8] Although RMA is frequently combined with SVR, the changes in regional myocardial wall stress in noninfarcted segments induced by the combined surgery have not been investigated sufficiently.

Multidetector computed tomography (MDCT) is an emerging technique that enables faster temporal resolution and more accurate contour definition. With ECG-gated image acquisition, cardiac MDCT shows different planes of the whole heart and enables the assessment of 3-dimensional volume and ejection performance. Recently, we have developed MDCT-based analysis software for computing local circumferential myocardial stress.[9]

The objective of the present study was to assess changes in LV volume and function and in regional myocardial stress in noninfarcted segments before and after RMA with or without

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Table 1. Patient Characteristics

Variables	RMA	RMA+SVR
No. of patients	18	21
Age, y	63±10	65±9
Male	14 (78)	17 (81)
Body surface area, m^2	1.64±0.19	1.61±0.17
NYHA class	3.0±0.3	3.2±0.7
LVEF		
0–0.15	3 (17)	2 (10)
0.16–0.25	4 (22)	11 (52)
0.26–0.35	11 (61)	8 (38)
LVEDD, mm	66±6	66±8
LVESD, mm	56±6	56±11
Coronary disease		
1 Vessel	3 (17)	4 (19)
2 Vessels	7 (39)	7 (33)
3 Vessels	6 (33)	8 (38)
LMT	2 (11)	2 (10)
Hypertension	14 (78)	11 (52)
Hyperlipidemia	11 (61)	10 (48)
Diabetes mellitus	10 (56)	10 (48)
Chronic renal insufficiency	3 (17)	6 (29)
Peripheral arterial disease	0	1 (5)
Cerebrovascular disease	2 (11)	1 (5)
COPD	2 (11)	3 (14)
Atrial fibrillation/flutter	6 (33)	5 (24)
History of ventricular tachycardia	1 (6)	3 (14)
Previous ICD	0	1 (5)
Previous PCI	11 (61)	8 (38)
Previous CABG	1 (6)	3 (14)

RMA indicates restrictive mitral annuloplasty; SVR, surgical ventricular restoration; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LMT, left main trunk; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter-defibrillator; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass grafting.

Data are presented as mean±SD or No. of patients (%).

SVR, in patients with ischemic cardiomyopathy (ICM) and functional mitral regurgitation (MR), using cine-MDCT and the software we developed.

Methods

Patients

Thirty-nine patients with ICM and functional MR (grade 3+ or greater) were referred for surgery. All had congestive heart failure symptoms, a history of at least 1 hospitalization, anterior/anteroseptal myocardial infarction, and advanced LV remodeling as defined by an LV ejection fraction (LVEF) ≤0.35 and an end-systolic volume >120 mL on preoperative left ventriculography. We excluded patients whose LV remodeling was less advanced or whose "ischemic" MR was secondary to a regional LV deformity caused by inferior/posterior myocardial infarction, or who had organic MR, a rheumatic mitral valve, or aortic valve disease. All patients were receiving optimized medical regimens, including β-blockers, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and diuretics. There were no significant between-group differences with respect to age, sex, body surface area, New York Heart Association (NYHA) functional class, LV dimension, or frequency of medical conditions listed, as shown in Table 1.

Table 2. Surgical Data

Variables	RMA (n=18)	RMA+SVR (n=21)
RMA	18	21
SVR	0	21
Ring size used		
Physio annuloplasty ring #24	12	10
Physio annuloplasty ring #26	6	11
Concomitant procedure		
CABG	15	11
TAP	15	13
Maze	2	2
PV isolation	3	3
Intraoperative data, min		
CPB time	218±64	246±102
AXC time	110±32	105±32

RMA indicates restrictive mitral annuloplasty; SVR, surgical ventricular restoration; CABG, coronary artery bypass graft; TAP, tricuspid annuloplasty; PV, pulmonary vein; CPB, cardiopulmonary bypass; and AXC, aortic cross-clamp.

Data are presented as mean±SD or No. of patients.

Of the 39 patients enrolled, 18 underwent RMA alone (RMA group), and the remaining 21 underwent RMA and concomitant SVR (RMA+SVR group). SVR was performed when broad anterior or anteroseptal akinetic or dyskinetic wall motion with wall thinning was detected by echocardiography. Selection between SVR procedures was based primarily on the preference of the surgeons (K. Taniguchi and T.S.). Coronary artery disease was treated either with CABG or percutaneous coronary intervention before surgery. Postoperative MR was none or trivial in all patients.

For comparative purposes, 38 subjects (26 men, 12 women; age range 49 to 82 years, mean 66±11 years) who did not have significant valvular or congenital cardiac disease, history of myocardial infarction, coronary artery lesions, or abnormal findings by echocardiography volunteered to participate in the study. Our institutional ethics committee approved this study, and written informed consent for all procedures was obtained from all patients before surgery.

Surgical Procedures

Surgeries were performed through a median sternotomy under mild hypothermic cardiopulmonary bypass with antegrade and retrograde intermittent cold blood cardioplegia. All patients underwent a stringent RMA (2 to 4 ring sizes smaller than measured; Table 2) with a semirigid ring (Carpentier-Edwards Physio ring; Edwards Lifesciences, Irvine, CA). SVR was performed with a Dor-type procedure with a Fontan stitch to eliminate anterior/anteroseptal dyskinetic scar tissue (akinetic or paradoxically expanding) of the LV with the goal of restoring the normal LV elliptical shape as much as possible.[10] Great care was taken not to injure the residual contractile myocardium. Simultaneous CABG nearly always involved grafting the left internal thoracic artery to the left anterior descending artery.

Cine-MDCT Angiography, Image Acquisition, and Data Processing

ECG-gated MDCT examinations of the heart were performed 1 month before surgery and repeated an average of 2.8 months (range 1.4 to 5.0 months) after surgery with a commercially available 64-slice multidetector scanner (SOMATOM Definition Dual Source CT, Siemens, Germany). No premedication with β-blockers to reduce the heart rate was used. Scans were performed during a single breath hold and lasted approximately 6 to 10 seconds or less. Patients were instructed to maintain an end-inspiratory breath hold, and data acquisition was begun.

Computed tomographic data of the entire heart were reconstructed with retrospective ECG gating and a standard cardiac algorithm.

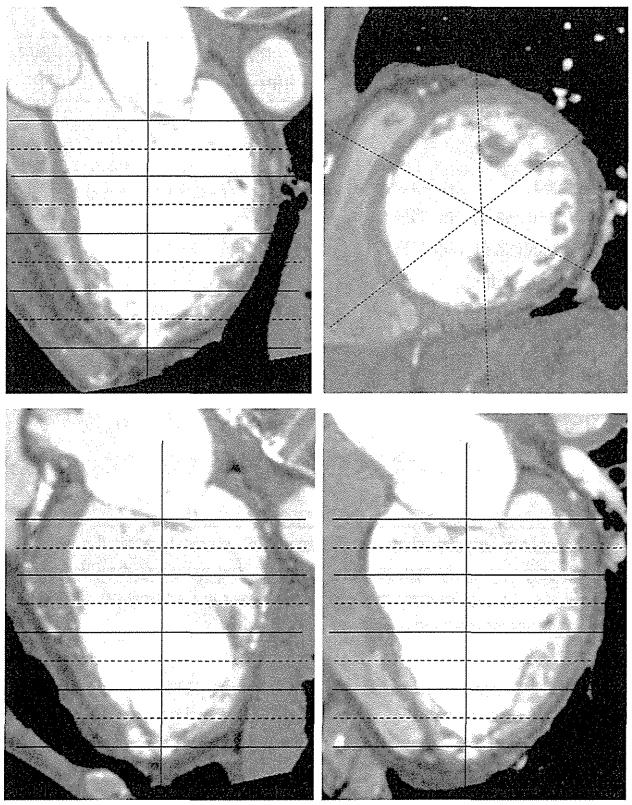

Figure 1. Long-axis views of the left ventricle extracted from a contrast-enhanced multidetector computed tomography data set: 3-chamber (top left), 2-chamber (bottom left), and 4-chamber (bottom right) views with the long axis of the ventricles, and a basal short-axis view with the location of the 3 long-axis imaging planes superimposed (top right).

From early systole to late diastole, 10 or 20 image series were reconstructed at 5% or 10% R-R interval increments throughout the cardiac cycle (5% to 95%). Routine LV function variables, such as LV end-diastolic volume, LV end-systolic volume, and LVEF were measured and calculated according to the slice summation method by manually drawing the endocardial and epicardial contours of short-axis images on a workstation using LV functional analysis software (Aquarius Net Station version 1.5, TeraRecon, Inc, San Mateo, CA). The end-diastolic and end-systolic phases were identified visually on the images that showed the largest and smallest LV cavity areas, respectively. The LV endocardial and epicardial borders were traced manually at end diastole and end systole. The papillary muscles and trabeculae were included in the chamber volume to obtain smooth endocardial contours suitable for shape analysis.

For the regional stress computation, the long-axis 2-, 3-, and 4-chamber and basal short-axis imaging planes of the LV were extracted from a contrast-enhanced MDCT data set in cine mode (Figure 1). A set of 3 long-axis imaging planes was oriented radially with 60° separations between them. The long axis of the LV was reconstructed by connecting the most apical point of the LV (apex) and the center of the basal short-axis LV image at end systole. These images were acquired as audio-video interleave or bitmap files. All image processing was verified by experienced radiologists (M.K. and S.H.).

LV Pressure Estimation

Blood pressure was obtained by a digital sphygmomanometer before the MDCT examinations. The LV end-systolic pressure (LVESP) was calculated for patients without significant MR (≥3+/4+) as LVESP=1.0×mean arterial cuff pressure+7 mm Hg and estimated in patients with significant MR as LVESP=0.98×mean arterial cuff pressure+11 mm Hg.[11]

Assessment of Regional Myocardial Wall Stress

The imaging analysis to assess regional myocardial stress was performed on a personal computer with dedicated analysis software (Osaka University-OSCAR STRESS tool, Osaka, Japan). LV end-diastolic volume, LV end-systolic volume, and LVEF were measured according to the slice summation method by manually drawing the endocardial and epicardial contours of short-axis images. LV volumes were indexed for body surface area. Intraobserver variability (Y. Shudo) and interobserver variability (Y. Shudo versus K. Takeda) for LVEDVI, LVESVI, and LVEF were evaluated with images obtained from 20 subjects.

The imaging analysis to assess regional end-systolic wall stress (ESS) was performed on a personal computer with dedicated analysis software for myocardial stress estimation. The software can measure regional ESS along 100 chords evenly spaced along the epicardial border in each image (Figure 1). In the present study, to simplify the display and analysis of regional ESS, 3 LV levels (base, mid-LV, and apex) were determined with reference to the long axis, and 3 perpendicular short axes were set at equal intervals. The regional ESS in the apical infarcted level was excluded from the present study because this region might be excluded by SVR. Regional ESS was calculated by averaging the value at consecutive local chords within each level.

Regional ESS was computed with the Janz formula (Equation 1) as[12]:

$$\text{Regional ESS} = P \times \Delta A_C / \Delta A_W \quad (1)$$

where P is end-systolic pressure, ΔA_C is the cross-sectional area of the LV cavity, and ΔA_W is the cross-sectional area of the LV wall at end systole in each long-axis plane. The wall cross-sectional area was defined as the area bounded by the 2 lines perpendicular to the cavity surface.[9] The average values of regional ESS for each element, eg, basal or mid-LV short axis slice, were then calculated for each patient.

For regional analysis of circumferential shortening, the 3 circular (basal, midcavity, and apical) short-axis slices of the LV were subdivided into 2 equal semicircular slices at the middle plane of each slice. The mean circumferential fiber shortening (CFS) was determined with the following equation:

$$\text{Mean CFS} = (\text{EDD} - \text{ESD})/\text{EDD}$$

where EDD is the end-diastolic short-axis dimension and ESD is the end-systolic short-axis dimension. The regional mean endocardial CFS was measured across the middle of each short-axis slice.

Echocardiography

Standard 2-dimensional and Doppler echocardiographic examinations with color-flow mapping were performed serially on all patients 1 week before and 2.0 months after the operation (GE Medical Systems, Vivid 7, Milwaukee, WI). Color-flow imaging was used to determine the presence or absence of MR, and the degree of MR was graded as follows based on the color Doppler echocardiography results at end systole: None to trivial (0 to 1+), mild (2+), moderate (3+), or severe (4+).[13] All echocardiographic data were analyzed in random order by trained readers who were blinded to the clinical data and timing of the echocardiogram.

Follow-Up

Patients were followed up in the hospital or outpatient clinic (by their primary cardiologist) at intervals of 3 to 6 months. The mean follow-up period for all patients was 685 days (range 75 to 1641 days). All 39 patients completed the follow-up examinations, which concluded on April 30, 2010. Although the follow-up period varied depending on the patient, there was no significant difference in the mean follow-up period between the 2 study groups (P=0.76).

The NYHA functional class and the clinical outcomes of death due to any cause or hospitalization for cardiac causes were recorded. The medical records of these patients were reviewed retrospectively for preoperative and postoperative data, and current information was obtained by interviewing the patient or the referring cardiologist.

Table 3. Hemodynamics and Left Ventricular Measurements

Variables	Controls (n=38)	RMA (n=18)			RMA+SVR (n=21)		
		Preoperative	Postoperative	Δ	Preoperative	Postoperative	Δ
Heart rate, bpm	67±12	74±12	74±10	NC	74±18	75±9	NC
Brachial artery pressure, mm Hg							
Systolic blood pressure	127±19	106±27†	113±20†	NC	103±12†	109±15†	NC
Diastolic blood pressure	70±12	64±11†	63±9†	NC	62±11†	64±11†	NC
Mean arterial pressure	89±13	78±18†	79±13†	NC	76±10†	79±11†	NC
End-systolic pressure	97±13	87±18†	86±13†	NC	85±10†	86±11†	NC
Global LV volume, mL/m^2							
LVEDVI	60±16	137±54†	108±31*†	−29±31	162±44†	105±34*†	−57±33‡
LVESVI	21±8	99±42†	72±31*†	−27±28	123±43†	71±31*†	−52±31‡
Global and regional systolic performance							
LVEF	0.65±0.07	0.27±0.08†	0.35±0.10*†	0.08±0.10	0.25±0.08†	0.35±0.12*†	0.11±0.09
Basal average CFS, circ^{-1}	0.38±0.05	0.15±0.04†	0.18±0.04*†	0.03±0.02	0.15±0.04†	0.18±0.03*†	0.03±0.03
Mid-LV average CFS, circ^{-1}	0.40±0.06	0.15±0.03†	0.17±0.03*†	0.02±0.02	0.16±0.06†	0.17±0.04*†	0.02±0.02
Regional circumferential end-systolic wall stress, kdyne/cm^2							
Basal ESS	186±56	308±110†	210±66*	98±120	359±183†	217±63*	141±184
Mid-LV ESS	170±57	287±86†	227±75*†	60±81	335±157†	220±60*†	115±139

RMA indicates restrictive mitral annuloplasty; SVR, surgical ventricular restoration; Pre, preoperative; Post, postoperative; Δ, postoperative value minus preoperative value; bpm, beats per minute; NC, not calculated; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; CFS, circumferential fiber shortening; and ESS, end-systolic circumferential myocardial stress.

Data are presented as mean±SD.

*$P<0.05$ for patients before vs after surgery.

†$P<0.05$ vs control.

‡$P<0.05$ for patients in RMA group vs patients in RMA+SVR group.

Statistical Analysis

SPSS (version 16.0, SPSS Inc) software was used for statistical analyses. Continuous values are expressed as mean±SD or mean value. Normally distributed variables were compared with Student *t* test for paired or unpaired data, and nonnormally distributed variables were compared by the Wilcoxon signed rank test or the Mann-Whitney *U* test. The MDCT-derived parameters (ie, LVEDVI, LVESVI, LVEF, CFS, and ESS) were analyzed over time with repeated-measures ANOVA. Categorical variables were analyzed by a χ^2 test or Fisher's exact test. Intraobserver and interobserver variabilities in the measurements of LV end-diastolic volume, LV end-systolic volume, and LVEF were analyzed by linear regression analysis. $P<0.05$ was considered statistically significant.

Results

Clinical Results

All patients tolerated the operation well. Mean NYHA functional class was significantly improved, from 3.0±0.6 to 2.0±0.8 ($P<0.001$). Mean NYHA functional class did not differ between the 2 groups ($P=0.36$ preoperatively and 0.73 postoperatively). During follow-up, 2 (11%) of 18 patients in the RMA group and 3 (14%) of 21 patients in the RMA+SVR group had recurrent congestive heart failure symptoms of NYHA functional class III or IV. The other patients remained well, with NYHA class I or II. The degree of MR was <2+ in all patients, a significant decrease (from 3.4±0.5 to 0.6±0.8; $P<0.0001$). During a mean follow-up of 23 months, the clinical outcome of death of any cause or hospitalization for cardiac causes occurred in 1 (5%) of 21 patients in the RMA group because of worsening congestive heart failure (n=1) and in 2 (11%) of 18 patients in the RMA+SVR group because of worsening congestive heart failure (n=1) and septic shock after infective endocarditis (n=1).

Intraoperative data are presented in Table 2. There were no significant differences in cardiopulmonary bypass time or aortic cross-clamp time between the 2 groups ($P=0.35$ and $P=0.55$, respectively). There were also no between-group differences in the type or size of the annuloplasty device used or the number of concomitant procedures ($P>0.05$ for all).

Heart Rates and Blood Pressure Measurements

As shown in Table 3, heart rates did not differ between the study groups and did not change postoperatively. Neither the preoperative nor the postoperative heart rates in the study groups differed from those in the controls.

Systolic and diastolic blood pressures and mean arterial and end-systolic pressures in both study groups and did not change postoperatively (Table 3). These blood pressures in the study groups both preoperatively and postoperatively were significantly lower than those in the controls.

LV Volumes

LV end-diastolic and end-systolic volume indexes (LVEDVI and LVESVI, respectively), which were markedly higher in both study groups preoperatively than in the controls ($P<0.0001$ for both), decreased significantly after surgery ($P<0.0001$ for both) but were still significantly higher than in the controls ($P<0.01$ for both; Table 3). Preoperative LVEDVI and LVESVI were significantly greater in the

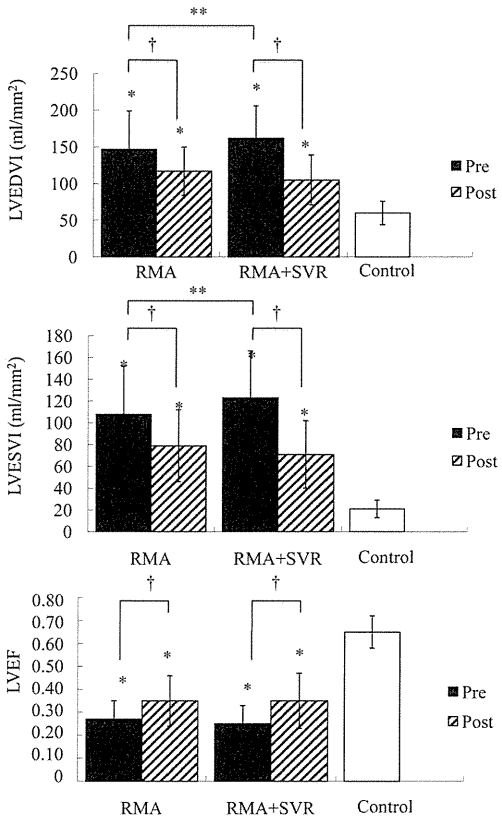

Figure 2. Preoperative (Pre; solid bar) and postoperative (Post; cross-hatched bar) left ventricular volumes and ejection fraction (LVEF) in patients in the restrictive mitral annuloplasty (RMA) and RMA plus surgical ventricular restoration (RMA+SVR) groups and the control group (open bar). †$P<0.05$ between preoperative and postoperative values. *$P<0.05$ vs control. **$P<0.05$ between patients in the RMA and RMA+SVR groups. LVEDVI indicates left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index.

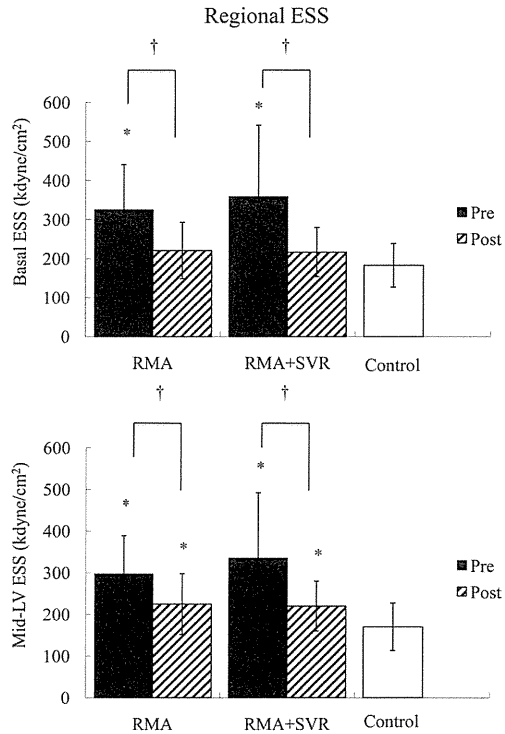

Figure 3. Preoperative (Pre; solid bar) and postoperative (Post; cross-hatched bar) regional end-systolic circumferential myocardial stress (ESS) in the basal and mid-left ventricular (mid-LV) regions in patients in the restrictive mitral annuloplasty (RMA) and RMA plus surgical ventricular restoration (RMA+SVR) groups and the control group (open bar). †$P<0.05$ between preoperative and postoperative values. *$P<0.05$ vs control.

RMA+SVR group than in the RMA group ($P<0.05$ for both), whereas the 2 groups' mean values for postoperative LVEDVI and LVESVI did not differ significantly as of 2.8 months' follow-up ($P>0.05$ for both; Figure 2).

Intraobserver and interobserver agreement for the measurements was assessed with the results from 20 subjects. Good correlation was shown for both the intraobserver (Y. Shudo; LVEDVI $r=0.92$, $P<0.001$; LVESVI $r=0.94$, $P<0.001$; LVEF $r=0.94$, $P<0.001$) and interobserver (Y. Shudo versus K. Takeda; LVEDVI $r=0.93$, $P<0.001$; LVESVI $r=0.95$, $P<0.001$; LVEF $r=0.89$, $P<0.001$) agreement.

Global and Regional Systolic Performance

Global LVEF, which was severely impaired in both study groups preoperatively, showed a significant increase postoperatively ($P<0.001$, respectively; Table 3). Global LVEF in the study groups both preoperatively and postoperatively was significantly lower than in the controls ($P<0.01$, respectively). There was no significant difference between the 2 study groups ($P<0.05$ both preoperatively and postoperatively; Figure 2).

The mean regional CFS in both the basal and mid-LV regions, which was reduced in both study groups preoperatively compared with controls ($P<0.001$, respectively), also increased significantly postoperatively ($P<0.001$, respectively) but was still significantly lower than in the controls ($P<0.01$, respectively). There was no significant difference in either region between the 2 study groups ($P>0.05$ for all).

Regional Circumferential ESS

Preoperatively, regional ESS was markedly elevated in both the basal and mid-LV regions of the LV in both the RMA and RMA+SVR groups compared with the corresponding regions in the controls ($P<0.001$, respectively; Table 3). At the basal region, regional ESS decreased significantly by an average of 142 kdyne/cm^2, from 359 to 217 kdyne/cm^2 (a reduction of 39%) in the RMA+SVR group, and by an average of 98 kdyne/cm^2, from 308 to 210 kdyne/cm^2 (a reduction of 32%) in the RMA group. At the mid-LV region, regional ESS significantly decreased by an average of 115 kdyne/cm^2, from 335 to 220 kdyne/cm^2 (a reduction of 34%) in the RMA+SVR group, and by an average of 60 kdyne/cm^2, from 287 to 227 kdyne/cm^2 (a reduction of 21%) in the RMA group, but the values remained significantly higher for both groups than in the controls ($P<0.01$; Figure 3).

Magnitude of Changes in Global LV Volume, LVEF, and Regional ESS

The percent reductions in LVEDVI and LVESVI were significantly larger in the RMA+SVR group than in the RMA group: $-35\pm20\%$ versus $-21\pm22\%$ for LVEDVI ($P=0.003$) and $-42\pm25\%$ versus $-27\pm28\%$ for LVESVI

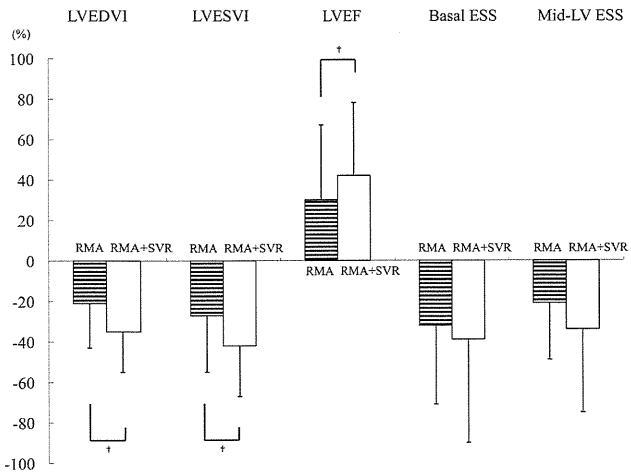

Figure 4. Magnitude of changes in global left ventricular volume, left ventricular ejection fraction (LVEF), and regional end-systolic circumferential myocardial stress (ESS) in the basal and mid-left ventricular (mid-LV) regions in patients in the restrictive mitral annuloplasty (RMA; ▤) and RMA plus surgical ventricular restoration (RMA+SVR; open bar) groups. †$P<0.05$ between RMA group and RMA+SVR group. LVEDVI indicates left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index.

($P=0.006$). The percent improvement in LVEF was significantly larger in the RMA+SVR group than in the RMA group (42±36% versus 30±37%, $P=0.01$).

The percent reduction of regional ESS in the basal and mid-LV regions tended to be greater in the RMA+SVR group than in the RMA group, although these differences did not reach statistical significance as of 2.8 months after the operation, which reflects the fact that the 2 procedures have different degrees of effects (Figure 4).

Discussion

The major findings of the present study are as follows: (1) LVEDVI and LVESVI were significantly greater in the RMA+SVR group than in the RMA group preoperatively, but they did not differ significantly between the 2 groups postoperatively. (2) LVEDVI and LVESVI decreased significantly, by 21% and 27% after RMA and by 35% and 42% after RMA+SVR, and the percent reductions in LVEDVI and LVESVI were significantly larger in the RMA+SVR group than in the RMA group. (3) Regional ESS and CFS improved significantly in the noninfarcted regions after RMA with or without SVR. The present findings indicated that RMA+SVR had a potentially greater effect in reducing LVEDVI and LVESVI than RMA. Although the role of concomitant SVR at the time of RMA is still controversial and no clear guidelines exist, the present results suggest that selected patients with advanced LV remodeling may benefit from concomitant RMA and SVR. The present data also suggest that regional dysfunction of the residual noninfarcted myocardium is at least partly reversible, although it is unknown whether this reversal is related to the alteration in contractility.

The present study focused on the LV volumetric change, measured by use of MDCT images, associated with RMA with or without SVR in patients with functional MR and ICM. In this small series, the addition of SVR resulted in a significantly greater degree of reduction in LV volume than was achieved with RMA alone. Although this difference might be explained by an additive effect of SVR with RMA, or as a function of the significantly greater preoperative values in this group, it is possible that this effect could contribute to the restoration of anterior/anteroseptal infarcted myocardium. In addition, our results showed that the postoperative LVEDVI and LVESVI were not different between the 2 study groups, which indicates either that SVR does not have a significant effect beyond RMA alone or that SVR is only useful in patients with a more severely dilated LV. However, future studies that control for the preoperative LV volume will be necessary to address this question. Data from a number of studies support the efficacy and use of SVR.[2,7,14,15] Many of these studies have demonstrated that in selected patients with ICM, ventricular reconstruction with various techniques can be accomplished with low operative mortality, improved LV volumes and function, and improved exercise capacity, quality of life, and NYHA class, along with reduced incidents of rehospitalization and good midterm survival.[2,7,14–17]

The recent Surgical Treatment for Ischemic Heart Failure (STICH) trial, which was randomized, concluded that the combination of SVR with CABG results in greater clinical benefits than CABG alone.[4] However, despite the larger reduction in LV end-systolic volume index obtained in their study (19% versus 6%),[4] the findings are strongly debated, largely because the SVR-related volume reductions were much smaller than in other SVR trials (typically 40%).[18] In the present results, the LV end-systolic volume index decreased by 42% (52±31 mL/mm^2) in the SVR+RMA group as of 2.8 months after the operation, which is in line with most previous studies at midterm follow-up, for example, the RESTORE (Reconstructive Endoventricular Surgery returning Torsion Original Radius Elliptical shape to the left ventricle) group (57±34 mL/mm^2),[2] Dor and coworkers (51±18 mL/mm^2),[16] and Di Donate and associates (average of 3 groups: 44±20 mL/mm^2).[17]

The adverse effects of LV dilatation were codified by White and associates,[19] who showed that increased ventricular volume rather than altered ejection fraction became the principal surrogate for mortality, regardless of whether the patient had significant residual coronary artery obstruction. In the present study, even when the LV was severely dilated, our approach (ie, RMA with SVR) was successful, resulting in LV volumetric reduction, wall stress reduction, attenuated LV ejection performance, improved symptoms, and satisfactory early results. These results were similar to those of RMA without SVR in patients with a less dilated LV. These findings may reflect the role of additional SVR as a surrogate for a more severe natural history of increasing morbidity and mortality in dilated hearts, although it is still unknown whether these surgical interventions improve the clinical status of the patient. Therefore, we assume that for selected patients with functional MR who have broad akinesia or dyskinesia associated with relative wall thinning, RMA with SVR is a reasonable surgical option that may prove beneficial.

Previous studies showed that hemodynamic improvement induced by SVR may depend on a complex interplay of changes in LV volume and LV wall stress.[7,8] It is possible that

reverse remodeling may happen in the border zone and induce further improvement in myocardial function.[20] However, chronic changes in myocardial stress, especially in the noninfarcted myocardium, after RMA with or without SVR have not been fully investigated, because it can be difficult to measure regional myocardial stress in LVs with different shapes. In the present study, we attempted to assess the changes in regional myocardial stress after RMA with or without SVR in patients with ICM and functional MR. We observed that regional ESS in the noninfarcted myocardium decreased substantially after RMA with or without SVR. We also observed that regional CFS improved in the same 2 regions after surgery. The present data suggest that regional dysfunction of the residual noninfarcted myocardium may be reversible, at least in part, although whether the improvement is related to the reduction in myocardial wall stress or to an alteration in the myocardial contractile property itself still needs to be evaluated.

Recent advances in steady-state free precession sequencing for cardiac MDCT have resulted in a shorter acquisition time and improved image quality. Considering the relatively short acquisition time and adequate quality of the reconstructed images, 64-row MDCT is a useful clinical tool for assessment of the LV contour in patients with ICM and functional MR.[21] The present study provides an additional approach for evaluation of LV volume, ejection performance, and wall stress, either globally or regionally. Echocardiography has been widely used to measure LV volume in heart failure, but the results are based on geometric assumptions that limit the accuracy of the data. Currently, cardiac magnetic resonance imaging (MRI) is considered the "gold standard" for LV geometry and volume evaluation.[22] It provides excellent temporal and spatial resolution, along with a high degree of accuracy, and reproducible quantitative measurements. Multiphase cine imaging quality is significantly better in MRI than in MDCT because of differences in temporal resolution. However, MRI requires an extended scanning period and cannot be used for patients with a pacemaker. Previous computed tomography studies have shown a good correlation and acceptable agreement of LV volumes and cardiac function compared with MRI.[23,24] This is probably because LV volumes and cardiac function are mainly determined by the end-systolic and end-diastolic phases, when cardiac motion is comparatively minimal and motion artifacts are negligible. Therefore, 64-row MDCT appears to be a useful alternative to 2-dimensional or 3-dimensional echocardiography or MRI in this study population with metal implants (eg, pacemakers or implantable cardioversion-defibrillators), claustrophobia, or other conditions that are not suitable for MRI.

Clinical Implications

On the basis of the present results in patients undergoing RMA who have ICM and functional MR, we favor combining RMA with SVR to exert an additional LV reverse-remodeling effect. In the present study, even when the LV was severely dilated, our approach was successful, and the early results are satisfactory.

Study Limitations

The major limitations of the present study are that it was not conducted in a randomized manner and that it involved a rather small sample size. However, the 100% patient follow-up is a strength. The study would have been stronger with a larger, randomized, and controlled population. In addition, the small sample size could place the study at risk for a type II error. Because we used each patient's preoperative data as his or her baseline, the statistical power was optimized.

Next, the preoperative LV volume differences between the 2 study groups might involve a probable selection bias toward SVR in patients with larger hearts; however, all the patients met the optimal entry criteria, which were the same as in previous studies.[2–5]

Regarding the technical aspects, the variety of surgical procedures and type of annuloplasty ring could have influenced the outcomes. SVR is still not a standardized technique, however, and the optimal procedure remains to be investigated. Concomitant procedures, especially CABG, might have favorably influenced our patients' LV functional improvements. The STICH trial report[4] showed that in 212 patients with LVEF <35% undergoing CABG alone, the mean end-systolic volume index at 4 months after surgery had decreased by an average of 5 mL/m^2, from 82 to 77 mL/m^2 (6% reduction), which indicates that there were no measurable functional improvements in those patients. Moreover, we previously observed no significant improvements in LV volumes, regional stress, or regional CFS in the noninfarcted myocardium at 8 months after CABG alone in patients with severe LV dysfunction.[15] Therefore, we think that the effect of revascularization could be minimized in the present results. Comparison of the fraction of patients who received concomitant CABG in each study group in the present series (RMA versus RMA+SVR; 83% versus 52%) suggests that there was little influence on LV volume, LVEF, or regional stress. However, differences may become obvious with further follow-up, because revascularization effects can be delayed well beyond 3 months in the failing ventricle.[25] We preferably used a semirigid complete annuloplasty ring. A previous report suggests that the type of annuloplasty ring could influence the postoperative LV function[26]; therefore, the present results would not be applicable to patients who received another type of prosthesis. Our results were obtained only from patients who underwent RMA with or without SVR, but the study did not include a control group of patients who did not have either procedure, and withholding surgery from such patients would be unethical in any case. To differentiate between the effects of RMA and SVR, future investigations that include other study groups to compare with patients undergoing SVR to treat functional MR will be required. The patients enrolled in the present study all had ICM associated with anterior or anteroseptal infarction. Therefore, the present results are not applicable to patients with inferior or lateral infarctions or patients with nonischemic dilated cardiomyopathy.

Finally, we used 64-row MDCT as the image modality. As with conventional modalities, MDCT has inherent limitations, including the need for contrast medium and radiation exposure. However, its high spatial resolution enables us to closely estimate regional wall thickness and appropriately compare preoperative values with postoperative values, which makes it particularly useful for estimating regional

myocardial stress. Moreover, given the increased use of cardiac defibrillators or biventricular pacemakers in patients with heart failure, which contraindicate some modalities (eg, MRI), MDCT should prove useful for noninvasively assessing ventricular function, although this point would have been stronger if the results could have been compared with MRI measurements.

Differences in the patients' breath-holding positions between slices and the vertical motion of the mitral annulus can affect the reconstructed images. For this reason, we determined the LV contour by carefully obtaining data from the same plane, as much as possible, before and after surgery. Therefore, differences due to the breath-holding position in the present patient series were negligible, and 3-dimensional reconstruction of the intracardiac anatomy from a series of 2-dimensional images was feasible and clinically useful.

Conclusions

RMA with or without SVR reduced LV end-diastolic and end-systolic volume, which led to improved global ejection performance, reduced regional myocardial wall stress, and improved regional fiber shortening of the noninfarcted myocardium in patients with ICM and functional MR. We found that RMA with SVR reduced the LVEDVI and LVESVI more than RMA alone. In correctly selected patients with more advanced LV remodeling, concomitant SVR may favorably affect the LV reverse-remodeling process induced by RMA.

Acknowledgment

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Disclosures

None.

References

1. Di Donate M, Sabatier M, Dor V, Toso A, Maioli M, Fantini F. Akinetic versus dyskinetic postinfarction scar: relation to surgical outcome in patients undergoing endoventricular circular patch plasty repair. *J Am Coll Cardiol.* 1997;29:1569–1575.
2. Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, Di Donate M, Menicanti L, Almeida de Oliveira S, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, Moore W, McCarthy PM, Oz MC, Fontan F, Scott ML, Accola KA; RESTORE group. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilatation. *J Am Coll Cardiol.* 2004;44:1439–1445.
3. Menicanti L, Castelvecchio S, Ranucci M, Frigiola A, Santambrogio C, de Vincentiis C, Brankovic J, Di Donate M. Surgical therapy for ischemic heart failure: single-center experience with surgical anterior ventricular restoration. *J Thorac Cardiovasc Surg.* 2007;134:433–441.
4. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, Hill JA, Menicanti L, Sadowski Z, Desvigne-Nichens P, Rouleau JL, Lee KL; STITCH Hypothesis 2 Investigators. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med.* 2009;23:360:1705–1717.
5. Maxey TS, Reece TB, Ellman Pl, Butler PD, Kern JA, Tribble CG, Kron IL. Coronary artery bypass with ventricular restoration is superior to coronary artery bypass alone in patients with ischemic cardiomyopathy. *J Thorac Cardiovasc Surg.* 2004;127:428–434.
6. Mehra MR, Reyes P, Benitez RM, Zimrin D, Gammie JS. Surgery for severe mitral regurgitation and left ventricular failure: what do we really know? *J Card Fail.* 2008;14:145–150.
7. Di Donate M, Toso A, Dor V, Sabatier M, Barletta G, Menicanti L, Fantini F; RESTORE Group. Surgical ventricular restoration improves mechanical intraventricular dyssynchrony in ischemic cardiomyopathy. *Circulation.* 2004;109:2536–2543.
8. Tulner SA, Steendijk P, Klautz RJ, Bax JJ, Schalij MJ, van der Wall EE, Dion RA. Surgical ventricular restoration in patients with ischemic dilated cardiomyopathy: evaluation of systolic and diastolic ventricular function, wall stress, dyssynchrony, and mechanical efficiency by pressure-volume loops. *J Thorac Cardiovasc Surg.* 2006;132:610–620.
9. Shudo Y, Matsumiya G, Takeda K, Matsue H, Taniguchi K, Sawa Y. Novel software package for quantifying local circumferential myocardial stress. *Int J Cardiol.* 2011;147:134–136.
10. Dor V, Saab M, Coste P, Kornaszewska M, Montiglio F. Left ventricular aneurysm: a new surgical approach. *Thorac Cardiovasc Surg.* 1989;37:11–19.
11. Rozich JD, Carabello BA, Usher BW, Kratz JM, Bell AE, Zile MR. Mitral valve replacement with and without chordal preservation in patients with chronic mitral regurgitation: mechanisms for differences in postoperative ejection performance. *Circulation.* 1992;86:1718–1726.
12. Janz RF. Estimation of local myocardial stress. *Am J Physiol.* 1982;242:H875–H881.
13. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation.* 2001;103:1759–1764.
14. Mickleborough LL, Merchant N, Ivanov Joan, Carson S. Left ventricular reconstruction: early and late results. *J Thorac Cardiovasc Surg.* 2003;128:27–36.
15. Taniguchi K, Sakurai M, Takahashi T, Imagawa H, Mitsuno M, Nakano S, Kawashima Y, Matsuda H. Postinfarction left-ventricular aneurysm: regional stress, function, and remodeling after aneurysmectomy. *Thorac Cardiovasc Surg.* 1998;46:253–259.
16. Dor V, Civaia F, Alexandrescu C, Montiglio F. The post-myocardial infarction scarred ventricle and congestive heart failure: the preeminence of magnetic resonance imaging for preoperative, intraoperative, and postoperative assessment. *J Thorac Cardiovasc Surg.* 2008;136:1405–1412.
17. Di Donate M, Castelvecchio S, Kukulski T, Bussadori C, Giacomazzi F, Frigiola A, Menicanti L. Surgical ventricular restoration: left ventricular shape influence on cardiac function, clinical status, and survival. *Ann Thorac Surg.* 2009;87:455–461.
18. Buckberg GD, Athanasuleas CL. The STICH trial: misguided conclusions. *J Thorac Cardiovasc Surg.* 2009;138:1060–1064.
19. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation.* 1987;76:44–51.
20. Yu HY, Chen YS, Tseng WY, Chi NS, Wang CH, Wang SS, Lin FY. Why is the surgical ventricular restoration operation effective for ischemic cardiomyopathy? Geometric analysis with magnetic resonance imaging of changes in regional ventricular function after surgical ventricular restoration. *J Thorac Cardiovasc Surg.* 2009;137:887–894.
21. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, Pennell DJ. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance: are they interchangeable? *Eur Heart J.* 2000;21:1387–1396.
22. Kaji S, Nasu M, Yamamuro A, Tanabe K, Nagai K, Tani T, Tamita K, Shiratori K, Kinoshita M, Senda M, Okada Y, Morioka S. Annular geometry in patients with chronic ischemic mitral regurgitation: three-dimensional magnetic resonance imaging study. *Circulation.* 2005;112(suppl):I-409–I-414.
23. Reman SV, Shar M, McCarthy B, Garcia A, Ferketich AK. Multi-detector row cardiac computed tomography accurately quantifies right and left ventricular size and function compared with cardiac magnetic resonance. *Am Heart J.* 2006;151:736–744.
24. Wu YW, Tadamura E, Yamamuro M, Kanao S, Okayama S, Ozasa N, Toma M, Kimura T, Komeda M, Togashi K. Estimation of global and regional cardiac function using 64-slice computed tomography: a comparison study with echocardiography, gated-SPECT and cardiovascular magnetic resonance. *Int J Cardiol.* 2008;128:69–76.
25. Bondarenko O, Beek AM, Twisk JW, Visser CA, van Rossum AC. Time course of functional recovery after revascularization of hibernating myocardium: a contrast-enhanced cardiovascular magnetic resonance imaging. *Eur Heart J.* 2008;29:200–205.
26. David TE, Komeda M, Pollick C, Burns RJ. Mitral valve annuloplasty: the effect of the type on left ventricular function. *Ann Thorac Surg.* 1989;47:524–528.

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Induced Adipocyte Cell-Sheet Ameliorates Cardiac Dysfunction in a Mouse Myocardial Infarction Model : A Novel Drug Delivery System for Heart Failure

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Induced Adipocyte Cell-Sheet Ameliorates Cardiac Dysfunction in a Mouse Myocardial Infarction Model

A Novel Drug Delivery System for Heart Failure

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Background—A drug delivery system that constitutively and effectively retains cardioprotective reagents in the targeted myocardium has long been sought to treat acute myocardial infarction. We hypothesized that a scaffold-free induced adipocyte cell-sheet (iACS), transplanted on the surface of the heart, might intramyocardially secrete multiple cardioprotective factors including adiponectin (APN), consequently attenuating functional deterioration after acute myocardial infarction.

Methods and Results—Induced ACS were generated from adipose tissue–derived cells of wild-type (WT) mice (C57BL/6J), which secreted abundant APN, hepatocyte growth factor, and vascular endothelial growth factor in vitro. Transplanted iACS secreted APN into the myocardium of APN-knockout (KO) mice at 4 weeks. APN was also detected in the plasma of iACS-transplanted APN-KO mice at 3 months (245±113 pg/mL). After left anterior descending artery ligation, iACS, generated from either WT (n=40) or APN-KO (n=40) mice, were grafted onto the surface of the anterior left ventricular wall of WT mice, or only left anterior descending artery ligation was performed (n=43). Two days later, inflammation and infarct size were significantly diminished only in the WT-iACS treated mice. One month later, cardiomyocyte diameter and percent fibrosis were smaller, whereas ejection fraction and survival were greater in the WT-iACS treated mice compared with the KO-iACS–treated or nontreated mice.

Conclusions—Cardioprotective factors including APN, hepatocyte growth factor, and vascular endothelial growth factor were secreted from iACS. Transplantation of iACS onto the acute myocardial infarction heart attenuated infarct size, inflammation, and left ventricular remodeling, mediated by intramyocardially secreted APN in a constitutive manner. This method might be a novel drug delivery system to treat heart disease. **(*Circulation*. 2011;124[suppl 1]:S10–S17.)**

Key Words: acute myocardial infarction ■ adiponectin ■ cell therapy ■ drug delivery system ■ tissue engineering

Despite recent progress in medical and surgical treatments for heart failure, acute myocardial infarction (AMI) and the subsequent deterioration of cardiac performance is still a major cause of death, worldwide. An array of cardioprotective reagents have been identified to be effective in ameliorating AMI by administrating into the infarcted myocardium in experimental models.[1] However, these reagents have failed to show consistent therapeutic efficacy in several clinical trials, probably due to poor retention or rapid inactivation of reagents in the injured myocardial tissues.[1] Therefore, a drug delivery system (DDS) that retains cardioprotective reagents in the targeted myocardial area has long been sought.

Intramyocardially transplanted autologous stem cells secrete various cardioprotective cytokines and growth factors, enhance angiogenesis, reduce fibrosis, attenuate apoptosis, and suppress myocyte hypertrophy, consequently ameliorating AMI in a paracrine manner.[2,3] However, cell transplantation for AMI has shown only modest therapeutic efficacy in large-scale clinical studies. It appears to result from insufficient paracrine effects whose magnitude and figure are largely affected by the cell delivery method or transplanted cell source.[4] To enhance the survival and functions of the transplanted cells, we developed a cell-sheet–based delivery method in which isolated cells, cultivated in vitro as a sheet without a scaffold, are simply placed on the surface of the myocardium. This treatment enhances the paracrine effects, resulting in better therapeutic efficacy.[5,6]

Adipocytes differentiated from adipose tissue–derived stromal-vascular fraction (SVF) cells are a promising cell

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