Does early surgical intervention improve left ventricular mass regression after mitral valve repair for leaflet prolapse?

John M. Stulak, MD, Rakesh M. Suri, MD, DPhil, Joseph A. Dearani, MD, Harold M. Burkhart, MD, Thoralf M. Sundt III, MD, Maurice Enriquez-Sarano, MD, and Hartzell V. Schaff, MD

Background: Left ventricular hypertrophy is associated with adverse cardiovascular outcomes. It is unclear whether hypertrophy caused by severe chronic mitral regurgitation regresses after mitral valve repair and, if so, which factors promote reverse remodeling and influence its prognostic significance.

Methods: Between March 1995 and December 2005, 2589 patients had mitral valve repair. Five hundred thirty patients (346 of whom were male) underwent isolated repair for leaflet prolapse and had echocardiographic data available from which the left ventricular mass index could be calculated. Concomitant preoperative tricuspid valve regurgitation was more than mild in 95 (18%) patients. Those with preoperative atrial fibrillation and other cardiac pathologies necessitating intracardiac repair were not included.

Results: Significant regression of left ventricular mass index occurred during the first 3 years (-28 g/m^2 , $P < .001$) and was maintained during follow-up for more than 3 years (-26 g/m^2 , $P < .001$). Higher preoperative left ventricular ejection fraction and greater preoperative left ventricular mass index independently predicted improved left ventricular mass index regression at 3 years. During follow-up of greater than 3 years, greater preoperative left ventricular mass index persisted in predicting improved mass regression ($P < 0.001$), and greater than mild preoperative tricuspid valve regurgitation was associated with less mass regression ($P < .001$). Late recovery of normal left ventricular ejection fraction was impaired in those with the greatest residual left ventricular mass; however, there was no difference in late symptoms or survival.

Conclusions: Performing mitral valve repair before a decrease in left ventricular ejection fraction and the development of significant secondary tricuspid valve regurgitation is associated with a greater likelihood of significant regression of left ventricular mass, possibly predicting improved recovery of normal left ventricular function after surgical intervention. These data provide additional support for early degenerative mitral valve repair. (J Thorac Cardiovasc Surg 2011;141:122-9)

Although recovery of normal left ventricular (LV) geometry and function via favorable LV remodeling is known to occur after mitral valve repair,^{1,2} it is unclear whether significant LV mass regression proceeds concurrently and, if so, which factors predict improved long-term normalization of left ventricular hypertrophy (LVH). It is known that incomplete regression of LV mass is associated with poor long-term outcomes after aortic valve replacement for aortic stenosis³⁻⁶ and during medical therapy for hypertension.⁷⁻⁹

The goals of this study were to document changes in left ventricular mass index (LVMI) after isolated mitral valve repair for leaflet prolapse and to identify factors influencing

favorable LV remodeling. We also sought to correlate the regression of LVMI with late outcomes, including recovery of normal left ventricular ejection fraction (LVEF), functional status, adverse cardiac events, and survival, to determine its prognostic significance.

MATERIALS AND METHODS

The Mayo Foundation Institutional Review Board approved this study, and all patients or their families provided written informed consent.

Patients

From March 1995 to December January 2005, 2589 patients had mitral valve repair at Mayo Clinic in Rochester, Minnesota. Of these, we identified 530 patients (346 men; median age, 63 years; range, 22–89 years) who underwent mitral valve repair for severe mitral regurgitation (MR) caused by isolated leaflet prolapse and who had echocardiographic data available from which LVMI could be calculated. We included those who had coexistent, clinically silent, functional tricuspid valve regurgitation (TR) that was less than severe, not associated with right heart failure symptoms or significant right ventricular dysfunction, and not related to a structural tricuspid valve abnormality. Patients with MR caused by congenital abnormalities, rheumatic or ischemic heart disease, or endocarditis resulting in leaflet destruction were excluded from this study. We also excluded those with a preoperative history of atrial fibrillation or concomitant cardiac pathology necessitating combined operations at the time of mitral valve repair.

From the Division of Cardiovascular Surgery, Mayo Clinic and Foundation, Rochester, Minn.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Read at the 90th Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, May 1–5, 2010.

J.M.S. and R.M.S. contributed equally.

Received for publication May 4, 2010; revisions received July 20, 2010; accepted for publication Aug 15, 2010.

Address for reprints: Rakesh M. Suri, MD, DPhil, Division of Cardiovascular Surgery, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (E-mail: suri.rakesh@mayo.edu).

0022-5223/\$36.00

Copyright © 2011 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2010.08.068

Abbreviations and Acronyms

- HR = hazard ratio
- LV = left ventricular
- LVEF = left ventricular ejection fraction
- LVH = left ventricular hypertrophy
- LVMI = left ventricular mass index
- MR = mitral regurgitation
- TR = tricuspid valve regurgitation

We chose to study a homogeneous population with MR caused by leaflet prolapse, which is the most frequent mitral valve pathology encountered in the Western world. This specific study period was chosen because techniques used during this era reflect our contemporary approach to mitral valve repair while ensuring capture of a representative follow-up period.

Clinical Characteristics

Preoperative TR was graded as none in 32 (6%) patients, trivial–mild in 403 (76%) patients, and moderate in 95 (18%) patients. The patient cohort did not have a high prevalence of significant comorbidities. Important preoperative clinical characteristics included hypertension in 193 (36%) patients, chronic obstructive pulmonary disease in 21 (4%) patients, and diabetes in 16 (3%) patients. Mitral valve pathology included isolated posterior leaflet prolapse in 286 (54%) patients, bileaflet prolapse in 212 (40%) patients, and isolated anterior leaflet prolapse in 32 (6%) patients.

Echocardiographic Analysis

Preoperative, postoperative, and follow-up evaluation of MR and TR was obtained by means of 2-dimensional and Doppler echocardiographic analysis. Severity of regurgitation was classified as 0 (none), 1 (trivial), 2 (mild), 3 (moderate), 3.5 (moderate–severe), and 4 (severe). LV mass was calculated with the corrected American Society of Echocardiography formula¹⁰ using 2-dimensional, M-mode, or 2-dimensional linear LV surface echocardiographic measurements. This calculation of LVMI is as follows:

$$LV\ mass\ (g) = 0.80[1.04\{PWT D + LVID + LISWT\}^3 - LVID^3] + 0.6.$$

The obtained result was indexed for body surface area in grams per square meter, with LVID defined as LV internal dimension in diastole, IVSD defined as interventricular septum dimension in diastole, and PWT D defined as posterior wall thickness in diastole. These methods have been validated in both animal models and human autopsy studies¹¹ and have been used in large population-based studies analyzing changes in LV mass in hypertensive patients.^{12,13} We defined the normal values for LVMI in this study as 71 g/m² for male patients and 60 g/m² for female patients, and LVH was considered present when LVMI was 134 g/m² or greater for male patients and 110 g/m² or greater for female patients.^{14,15} Taking into account the distribution of sex in this cohort, the calculated normal value used for LVMI overall in this study taken as a group was 67 g/m², and the criteria for LVH was 125 g/m² or greater. This was done by adding the product of the percentage of male patients and the normal LVMI value for male patients to the product of the percentage of female patients and the normal LVMI value for female patients.

Preoperative Data

Mean preoperative LVMI values are shown in Table 1, and mean preoperative New York Heart Association (NYHA) functional classes are shown in Table 2.

TABLE 1. Mean preoperative LVMI values

Patient group	No. of patients	LVMI (g/m ²)	Multiple of normal	P value
Entire cohort	530	128 ± 30	1.9	
Male patients		131 ± 28	1.8	
Female patients		120 ± 31	2.0	.56
Hypertension	193	128 ± 30	1.9	
No hypertension	337	127 ± 29	1.9	.89
LVMI terciles				
≤115 g/m ²	175	96 ± 14	1.4	
115–140 g/m ²	178	127 ± 7	1.9	
≥140 g/m ²	177	160 ± 19	2.4	.03
Preoperative TR				
None	32	115 ± 18	1.7	
Trivial–mild	403	128 ± 28	1.9	
Moderate	95	129 ± 42	1.9	.17

LVMI, Left ventricular mass index; TR, tricuspid valve regurgitation.

Statistical Analysis

Demographic and other patient-related data were obtained from Mayo Clinic medical records and our prospective clinical database. Follow-up information was obtained from subsequent clinic visits, written correspondence from local physicians, and mailed questionnaires to patients or families. Continuous data were expressed as either means ± standard deviations or medians with ranges. Risk factors were assessed by using log-rank analysis. Variables significant in the univariate analysis were used during stepwise selection to create the final multivariable model. Survival was determined by using Kaplan–Meier analysis. Early operative mortality was defined as death occurring within 30 days of the operation or at any time during the index hospitalization.

RESULTS

All patients underwent isolated mitral valve repair for severe MR caused by leaflet prolapse. The most commonly used techniques for mitral valve repair have been described elsewhere.^{16,17} The closing interval for this cohort was 3 months, and median echocardiographic follow-up was 3.5 years (maximum, 13.1 years). Echocardiographic data were grouped into the following categories: preoperative, 3 years or less, and greater than 3 years.

LV Mass Regression and LVEF

Significant regression of LVMI (all compared with baseline values) occurred during the first 3 years to a mean of

TABLE 2. Mean preoperative NYHA functional class

Patient group	NYHA class	P value
Entire cohort	1.9 ± 0.8	
Male patients	1.8 ± 0.8	
Female patients	2.1 ± 0.8	.4
Hypertension	2 ± 0.8	
No hypertension	1.8 ± 0.8	.32
LVMI terciles		
≤115 g/m ²	2 ± 0.9	
115–140 g/m ²	1.8 ± 0.7	
≥140 g/m ²	1.9 ± 0.9	.56

NYHA, New York Heart Association; LVMI, left ventricular mass index.

100 ± 25 g/m² (−28 g/m², $P < .001$) and stabilized at 100 ± 26 g/m² (1.5× normal value) during follow-up of longer than 3 years ($P < .001$, Figure 1). There was similar regression of LVMI for male patients (−31 g/m² at ≤3 years and −30 g/m² at >3 years, $P < .001$) and female patients (−23 g/m² at ≤3 years and −21 g/m² at >3 years, $P < .001$), with no significant difference between the groups ($P = .66$). Patients with preoperative hypertension had similar LVMI regression (−27 g/m² at ≤3 years and −31 g/m² at >3 years, $P < .001$) compared with that seen in patients without hypertension (−28 g/m² at ≤3 years and −25 g/m² at >3 years, $P < .001$); there was no significant difference between the groups ($P = .34$). We divided patients into terciles based on the degree of preoperative LVMI. At the 3 years or less and greater than 3 years time points, respectively, patients with preoperative LVMI in the 115 g/m² or less tercile had LVMI regression of −10 g/m² and −7 g/m² ($P = .88$), those with preoperative LVMI of 115 to 140 g/m² had regression of −29 g/m² and −28 g/m² ($P < .026$), and those in the 140 g/m² or greater tercile had regression of −47 g/m² and −43 g/m² ($P < .001$), respectively (Figure 2). By tercile, LVMI regressed to 1.3×, 1.5×, and 1.7× normal values, respectively. The incidence of recurrent moderate or greater MR was not significantly different among preoperative groups at both the 3 years or less (≤115 g/m², 3%; 115–140 g/m², 4%; and >140 g/m², 10%; $P = .34$) and greater than 3 years (≤115 g/m², 10%; 115–140 g/m², 10%; and >140 g/m², 12%; $P = .72$) time points.

At greater than 3 years' follow-up, patients with no preoperative functional TR had −26 g/m² regression of LVMI to 89 g/m² (1.3× normal value), whereas those with trivial to mild TR had LVMI regression of −28 to 100 g/m² (1.5× normal value). Those with moderate TR had LVMI regression of only −17 to 112 g/m² (1.7× normal value, $P < .001$,

FIGURE 1. Change in left ventricular (LV) mass index during follow-up intervals is shown. There is a significant decrease in LV mass index at 3 years or less and greater than 3 years compared with preoperative values ($P < .001$). Multiples of normal values are shown on the right.

FIGURE 2. Change in left ventricular mass index (LVMI) according to the degree of preoperative LVMI during follow-up intervals is shown. Less regression of LVMI was noted in the highest tercile cohort at 3 years or less and greater than 3 years compared with the lower 2 terciles ($P < .001$). Multiples of normal values are shown on the right.

Figure 3). The following variables were independently associated with greater LVMI regression during the first 3 years of follow-up: greater preoperative LVEF (hazard ratio [HR], −0.89 [95% confidence interval, −1.6, −0.2]; $P = .013$) and greater preoperative LVMI (HR, −0.59 [95% confidence interval, 0.75, −0.4]; $P < .001$). At follow-up past 3 years, greater preoperative LVMI remained independently associated with greater LVMI regression (HR, −0.55 [95% confidence interval, −0.72, −0.4]; $P < .001$), whereas moderate preoperative TR was predictive of significantly less LVMI regression (HR, 16.7 [95% confidence interval, 2.9, 30.5], $P = .017$).

Preoperative LVEF was 65%, 67%, and 65% in the 115 g/m² or less, 115 to 140 g/m², and greater than 140 g/m² groups, respectively. Within 3 years of follow-up, LVEF decreased to 61%, 59%, and 57% in the 115 g/m² or less, 115

FIGURE 3. Change in left ventricular (LV) mass index according to degree of preoperative tricuspid valve regurgitation (TR) during late follow-up at greater than 3 years is shown. There is a significant difference in LV mass index regression between patients with no and trivial–mild preoperative TR compared with that seen in patients with moderate preoperative TR ($P < .001$).

to 140 g/m², and greater than 140 g/m² LVMI tercile groups, respectively ($P = .06$). At follow-up of greater than 3 years, LVEF stabilized at 62% and 60% in the 115 g/m² or less and 115 to 140 g/m² groups, respectively, but continued to decrease in the greater than 140 g/m² group to 53% ($P = .007$; Figure 4, A). Similarly, LV end-systolic dimension was greatest in the highest LVMI tercile preoperatively. Whereas patients in the lowest 2 terciles had a decrease in LV end-systolic dimension with time, those with the greatest LVMI were significantly impaired in their ability to remodel toward more normal dimensions during follow-up (Figure 4, B).

NYHA Functional Class

For the entire cohort, NYHA functional class significantly improved from 1.9 ± 0.8 preoperatively to 1.4 ± 0.7 at last follow-up ($P < .001$); 70% of patients were in NYHA functional class I at follow-up (compared with 38% preoperatively, $P < .001$). Male patients had similar postoperative recovery of NYHA functional class I status

when compared with female patients ($P = .62$). Although patients in each tercile based on preoperative LVMI had significant improvement in NYHA functional class during follow-up, there was no significant difference among the 3 groups ($P = .64$).

Late Nonfatal Morbidity

Responses to follow-up questionnaires inquiring about late adverse events were obtained in 382 (72%) patients. Thirty-three (8.7%) patients were in NYHA functional class III or IV, and 2 (0.005%) patients had a late myocardial infarction. Seven (1.9%) patients underwent a reoperation on the mitral valve, and all but 1 patient had mitral valve re-repair. Overall actuarial freedom from late stroke was 96% at 10 years, which was similar between patients with (96%) and without (95%) preoperative hypertension ($P = .91$). Late freedom from stroke at 10 years was also not significantly different when stratified by preoperative LVMI tercile (≤ 115 g/m², 97%; 115–140 g/m², 98%; and ≥ 140 g/m², 93%; $P = .77$).

FIGURE 4. A, Change in left ventricular ejection fraction (LVEF) according to the degree of preoperative left ventricular mass index (LVMI) during follow-up intervals is shown. There is a significant difference in LVEF at greater than 3 years in the greater than 140 g/m² group compared with the 115 g/m² or less and 115 to 140 g/m² groups ($P < .001$). B, Change in left ventricular end-systolic dimension (LVESD) according to degree of preoperative LVMI during follow-up intervals is shown. There is a significant difference in LVESD at all time points ($P < .01$).

Late Survival

Median late follow-up for determination of vital status was 4.9 years (maximum, 13.1 years). Overall late actuarial survival for the entire cohort was 94.4% at 5 years and 81.1% at 10 years. Late survival was similar among patients within each tercile of preoperative LVMI: 94% at 5 years and 81% at 10 years for the 115 g/m² or less group, 94% at 5 years and 84% at 10 years for the 115 to 140 g/m² group, and 95% at 5 years and 79% at 10 years for the 140 g/m² or greater group ($P = .99$; Figure 5, A). Decreased preoperative LVEF (HR, 1.04 [1.02–1.11]; $P = .001$), advanced age (HR, 1.11 [1.08–1.13]; $P < .001$), and preoperative renal insufficiency (HR, 3.43[1.2–9.5];

FIGURE 5. Overall actuarial survival according to the degree of preoperative left ventricular mass index is shown. There is no significant difference between groups during late follow-up.

$P = .02$) were independently associated with decreased late survival.

DISCUSSION

Performing mitral valve repair for leaflet prolapse before a decrease in preoperative LVEF and the development of moderate functional TR predicts a greater likelihood of more complete regression of LVMI after surgical intervention. Although greater preoperative LVMI did result in greater percentage regression of LVMI during follow-up, these patients retained greater residual LVMI ($1.7 \times$ normal value) and had less recovery of normal LV function and dimensions when compared with those with less initial preoperative LVMI. Preoperative LVMI likely reflects the degree of adverse LV remodeling in patients with chronic MR and might help guide the timing of early mitral valve repair.

The effect of excess LV mass has perhaps been best studied in hypertensive patients and those with aortic valve stenosis. Regression of echocardiographic LVH during treatment for hypertension has been shown to reduce cardiac risk,¹⁸ whereas inappropriate or incomplete LV mass regression is associated with adverse outcomes and ventricular contractile dysfunction.¹⁹ Similarly, after aortic valve replacement for severe aortic stenosis, the most important predictor of diminished LV mass regression was the extent of preoperative LVMI, whereas survival and heart failure were not influenced by the extent of regression. Some have suggested that earlier surgical intervention for severe aortic valve stenosis might be the most important factor in facilitating postoperative normalization of LVMI; however, the potential effect on long-term survival must be studied further in the absence of definitive scientific evidence.²⁰

Prior data have established that early mitral valve repair before the onset of symptoms or LV dysfunction (LVEF $< 60\%$ or LV end-systolic dimension ≥ 40 mm) is important for normalization of late survival, optimization of reverse LV remodeling, and recovery of LVEF.^{1,2,21-23} Recent reports point to even more advanced indications for optimization of LV functional recovery. Enriquez-Sarano and Sundt²⁴ have recently published a formalized rationale for early mitral repair. First, because only a small fraction of patients remain alive and free from operation in the long-term after the diagnosis of organic mitral valve regurgitation, surgical intervention is largely unavoidable. Second, by the time class I indications for surgical intervention (LVEF $\leq 60\%$ or LV end-systolic dimension ≥ 40 mm) have been met, patients are already at significantly increased risk for higher overall mortality compared with those without symptoms.²⁵ Third, early mitral valve repair has been demonstrated to restore life expectancy to normal.²⁶ Fourth, patients with organic MR under medical management possess not only increased mortality²⁷ but have twice the risk of sudden death compared with the

general population.²⁸ Finally, there is no alternative medical treatment that is equivalent to early mitral valve repair.²⁴

Currently, the degree of LV mass is not included in the guidelines for the timing of mitral valve repair for severe MR.^{21,22} In this study, the following preoperative factors predicted less complete regression of LVMI after mitral valve repair: diminished preoperative LVEF, preoperative moderate functional TR, and greater degrees of preoperative LVMI. Not surprisingly, we found that regression of LVMI after mitral valve repair was accompanied by significant improvement in NYHA class during follow-up. Perhaps counterintuitive was the finding that functional improvement was also seen when patients were grouped according to degree of preoperative LV mass. The lack of association between incomplete LV mass regression and worse functional status has also been observed after aortic valve replacement for aortic stenosis.²⁰ To our knowledge, there are very few data demonstrating that poor LV mass regression is associated with impaired functional status after surgical correction of heart valve disease. Even though patients with the highest degrees of preoperative LVMI ($> 2 \times$ normal value) had incomplete reverse remodeling compared with those with lower LV mass, regression below the accepted cutoff point for the echocardiographic criteria of LVH still occurred. Similarly, we demonstrate that overall survival was not affected by incomplete LV mass regression, which has also been observed after aortic valve replacement.²⁰ The majority of information about LV mass and its relation to long-term survival comes from the hypertension literature,^{29,30} and although current evidence demonstrates poor long-term survival with LVH in these patients, there is little evidence that LV mass regression itself affects survival. In contrast, incomplete regression of LV mass has been associated with an increased risk of stroke, and some have suggested that reverse remodeling might decrease this risk.³¹ The major effect of incomplete LV mass regression demonstrated in the current series was failure of LV function to recover during late follow-up; patients with the greatest degree of preoperative LVMI ($> 2 \times$ normal value) had a significant and progressive decline in LVEF, whereas those with less preoperative LVMI benefitted from stabilization and recovery of LVEF over time.

Our understanding of the prognostic significance of preoperative LVH in patients with chronic MR is still nascent. Recently, Song and colleagues³² examined ventricular reverse remodeling early after mitral valve repair for severe MR in patients with concomitant atrial fibrillation. They sought to determine whether preoperative clinical, echocardiographic, and N-terminal B-type natriuretic peptide could predict postoperative LV reverse remodeling after mitral valve repair and a modified maze procedure. Important differences between their study and our own include the following: (1) all patients in the former study underwent a modified

maze procedure, and some also had tricuspid valve repair; (2) all patients had atrial fibrillation; and (3) there was important heterogeneity in the cause of mitral valve disease, including rheumatic pathology. Furthermore, in the study by Song and colleagues,³² patients with failure of LV mass regression were older and more likely to have preoperative hypertension, and preoperative N-terminal B-type natriuretic peptide negatively influenced the capacity for LV mass regression. Those who did undergo reverse remodeling did so early after surgical intervention, which correlated with progressive recovery of LVEF and normalization of LV end-diastolic/end-systolic dimensions during follow-up in a manner consistent with our prior investigations.¹ As Song and colleagues³² suggest, the capacity for favorable reverse ventricular remodeling might diminish with time as a consequence of prolonged exposure to chronic uncorrected MR, leading to irreversible pathologic fibrotic change and diminished mass regression, even after effective mitral valve repair. Our data support this hypothesis; those in the highest tercile of preoperative LV mass ($>2\times$ normal value) had both less effective regression of LV mass and diminished ejection fraction recovery with time.

Limitations

This study cohort is intentionally homogeneous to better understand the clinicopathologic relationship between LV mass and clinical/echocardiographic outcomes in a group of patients with isolated leaflet prolapse undergoing early isolated mitral valve repair. It is clearly understood that the results might not be generalizable to all patients undergoing mitral valve surgery. The patients in this study were also selected on the basis of having echocardiographic data available for LVMI calculations; others who met inclusion criteria but lacked this information were not included in this report. Follow-up questionnaires were obtainable in approximately 75% of patients, and although this represented the most complete effort possible, we recognize the fact that late data from one quarter of the patient cohort were not analyzed. Although the absence of this information might affect the detected prevalence of late events, we have no reason to believe that those who were lost to follow-up were systematically excluded for some distinguishing feature. It remains possible, however, that those who were available for clinical or echocardiographic follow-up had a higher prevalence of certain clinical features. Despite demonstrating that greater LV mass adversely affects the recovery of normal LV function, one possible reason we failed to identify an effect on clinical outcome might have been our programmatic adherence to a principle of early mitral valve repair surgery for severe MR before symptom onset or LV dysfunction. We acknowledge that data regarding the effectiveness of antihypertension or afterload reduction therapy after mitral valve repair in this study are sparse. We are currently planning studies to investigate the potential

role that these therapies might play in influencing LV mass regression after mitral valve repair surgery

CONCLUSIONS

Performing early mitral valve repair before the development of severe LVH greater than twice normal, decline in preoperative LVEF, or the development of significant functional TR is associated with an improved likelihood of significant regression of LV mass after surgical correction. Patients with the greatest degree of residual postoperative LV mass are limited in their ability to recover normal LV systolic function with time after mitral repair, although late functional capacity, adverse cardiac events, and survival do not appear to be affected in this preliminary analysis. These data provide additional support for early valve repair for leaflet prolapse to optimize favorable LV remodeling and recovery of normal LV systolic function.

References

1. Suri RM, Schaff HV, Dearani JA, et al. Recovery of left ventricular function after surgical correction of mitral regurgitation caused by leaflet prolapse. *J Thorac Cardiovasc Surg.* 2009;137:1071-6.
2. Ashikhmina EA, Schaff HV, Suri RM, Enriquez-Sarano M, Abel MD. Left ventricular remodeling early after correction of mitral regurgitation: maintenance of stroke volume with decreased systolic indexes. *J Thorac Cardiovasc Surg.* 2010;140:1300-5.
3. Maselli D, Pizio R, Bruno LP, Di Bella I, De Gasperi C. Left ventricular mass reduction after aortic valve replacement: homografts, stentless and stented valves. *Ann Thorac Surg.* 1999;67:966-71.
4. De Paulis R, Sommariva L, Colagrande L, et al. Regression of left ventricular hypertrophy after aortic valve replacement for aortic stenosis with different valve substitutes. *J Thorac Cardiovasc Surg.* 1998;116:590-8.
5. De Paulis R, Sommariva L, De Matteis GM, et al. Extent and pattern of regression of left ventricular hypertrophy in patients with small size Carbomedics valves. *J Thorac Cardiovasc Surg.* 1997;113:901-9.
6. Khan SS, Siegel RJ, DeRobertis MA, et al. Regression of hypertrophy after Carpentier-Edwards pericardial aortic valve replacement. *Ann Thorac Surg.* 2000;69:531-5.
7. De Simone G, Palmieri V, Koren M, Mensah G, Roman MJ, Devereux RB. Prognostic implications of the compensatory nature of left ventricular mass in arterial hypertension. *J Hypertens.* 2001;19:119-25.
8. de Simone G, Verdecchia P, Pedr S, et al. The MAVI study. *Hypertension.* 2002;40:470-6.
9. Muisan ML, Salvetti M, Pains A, et al. Inappropriate left ventricular mass changes during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension.* 2007;49:1077-83.
10. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18:1440-63.
11. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantification of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantification of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2:358-67.
12. Gottdiener JS, Bednarz J, Devereux R, et al. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. *J Am Soc Echocardiogr.* 2004;17:1086-119.
13. Devereux RB, Wachtell K, Gerds E, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA.* 2004;292:2350-6.
14. Abergel E, Tase M, Bohlender J, et al. Which definition for echocardiographic left ventricular hypertrophy? *Am J Cardiol.* 1995;75:498.

15. Devereaux RB, Tulas EM, Casale PN, et al. Standardization of M-mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol*. 1984;4:1222.
16. Suri RM, Schaff HV, Dearani JA, et al. Survival advantage and improved durability of mitral repair for leaflet prolapse subsets in the current era. *Ann Thorac Surg*. 2006;82:819-26.
17. Suri RM, Orszulak TA. Triangular resection for repair of mitral regurgitation due to degenerative disease. *Operat Tech Thorac Cardiovasc Surg*. 2005;10:194-9.
18. Pierdomenico SD, Lapenna D, Cuccurullo F. Regression of echocardiographic left ventricular hypertrophy after 2 years of therapy reduces cardiovascular risk in patients with essential hypertension. *Am J Hypertens*. 2008;12:464-70.
19. Zybach-Benz RE, Aeschbacher BC, Schwerzmann M. Impact of left ventricular hypertrophy late after aortic valve replacement for aortic stenosis on cardiovascular morbidity. *Int J Cardiol*. 2006;109:41-7.
20. Hanayama N, Christakis GT, Mallidi HR, et al. Determinants of incomplete left ventricular mass regression following aortic valve replacement for aortic stenosis. *J Card Surg*. 2005;20:307-13.
21. Enriquez-Sarano M, Tajik AJ, Schaff HV, et al. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: results and clinical implications. *J Am Coll Cardiol*. 1994;24:1536-43.
22. Matsumura T, Ohtaki E, Tanaka K, et al. Echocardiographic prediction of left ventricular dysfunction after mitral valve repair for mitral regurgitation as an indicator to decide the optimal timing of repair. *J Am Coll Cardiol*. 2003;42:458-63.
23. Adams DH, Anyanwu AC. Asymptomatic mitral regurgitation: does surgery save lives? *Nat Rev Cardiol*. 2009;6:330-2.
24. Enriquez-Sarano M, Sundt TM. Early surgery is recommended for mitral regurgitation. *Circulation*. 2010;121:804-12.
25. Tribouilloy C, Enriquez-Sarano M, Schaff HV, et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. *Circulation*. 1999;99:400-5.
26. Enriquez-Sarano M, Tajik A, Schaff HV, Orszulak TA, Bailey K, Frye R. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation*. 1994;90:830-7.
27. Ling H, Enriquez-Sarano M, Seward J, et al. Clinical outcome of mitral regurgitation due to flail leaflets. *N Engl J Med*. 1996;335:1417-23.
28. Grigioni F, Enriquez-Sarano M, Ling L, et al. Sudden death in mitral regurgitation due to flail leaflet. *J Am Coll Cardiol*. 1999;34:2078-85.
29. Casale PN, Devereaux RB, Milner M, et al. Value of echocardiographic left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med*. 1986;105:173-8.
30. Daider AW, Larson MG, Benjamin EJ, et al. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol*. 1998;32:1454-9.
31. Verdecchia P, Angeli F, Gattobigio R, Sardone M, Pede M, Reboldi GP. Regression of left ventricular hypertrophy and prevention of stroke in hypertensive subjects. *Am J Hypertens*. 2006;19:493-9.
32. Song BG, On YK, Jeon ES, et al. Ventricular reverse remodeling early after mitral valve repair for severe chronic mitral regurgitation with atrial fibrillation. *Cardiology*. 2009;114:132-41.

Discussion

Dr David H. Adams (*New York, NY*). By way of disclosure, I am an inventor with a royalty agreement with Edwards.

John, I would like to congratulate you on a job well done with your presentation and manuscript. We all admire the enormous contributions from the Mayo Clinic to our understanding of the timing for intervention in mitral valve disease, most recently summarized in an excellent review published earlier this year in *Circulation* by Maurice Sarano and our Secretary, Thor Sundt. Essentially, all the class I triggers for intervention in the guidelines, including LV end-systolic dimension, ejection fraction, and the development of symptoms, result from clinical research from the Mayo Clinic.

In this article you attempt to add significant LVH to the list of potential indications for valve repair in patients with prolapse. Although I agree with the benefit of operating on patients with severe regurgitation early in the course of their disease to protect the ven-

tricle, I am not convinced yet that your study has provided sufficient data to elevate LVH or the likelihood of ventricular remodeling to our list of triggers. I have a few questions.

You mentioned early surgical intervention in the title of your article, which is never really defined. I know your institution has been a leading proponent of early surgical intervention in asymptomatic patients with preserved LV function, and therefore I would like to understand your data in this context. Your landmark article first authored by Seano on this topic was published in 2005, yet surely many patients in this study were operated on in an early setting because that particular article took a few years to actually come out in print. The LVEF was 65% or greater in all 3 terciles, and you did you not see a difference in functional class between cohorts. Therefore there seems no clear indication that higher LVMI in selected patients reflected delayed surgical intervention. Can you tell us what exactly you define as early surgical intervention and also the proportion of patients in each tercile defined by LVMI who had early surgical intervention as you define it?

Dr Stulak. Thank you, Dr Adams. We appreciate you being our discussant. At Mayo Clinic, we operate on patients who are well within class I and class IIA indications; however, prior studies from our institution have demonstrated superior outcomes when operations are undertaken when the LVEF is between 60% and 65% and when the LV end-systolic dimension is between 36 and 40 mm. That is what we define as the criteria for early mitral valve repair.

Dr Adams. Can you tell us why LVMI was not quantifiable in approximately 15% of your cohort? You excluded about 15% of patients, saying you could not calculate LVMI. Can you tell us why that was and what your protocol was for defining it?

Dr Stulak. This study period was from 1995 to 2005. Standardization of the reporting of echocardiographic data did not become common practice until the late 1990s. Therefore the most commonly missed measurement was posterior wall thickness. For the calculation of LVMI, we used the equation set forth by the American Society of Echocardiography. I would surmise that those 15% of patients probably were lost during that lack of standardization time period.

Dr Adams. John, in another article from your institution this year, a preoperative LV end-systolic dimension of greater than 40 mm was identified as a predictor of late mortality after mitral valve repair. Why do you think a high LVMI was not associated with late mortality? Do you think hypertension in more than a third of your patients is the confounder that really explains this?

Dr Stulak. We were surprised at the finding that there is no difference in late survival, and I believe that there are several reasons to explain this finding. First, hypertension could have been a confounder; however, this was not found to be independently associated with a multivariable model. Furthermore, patients with and without hypertension had a similar degree of LV mass regression. Second, this is a retrospective study using historical echocardiographic data and obvious limitations exist. Third, it is a highly selected patient population with a single cause of MR. This lack of difference in survival actually is what has been observed in studies examining patients with aortic stenosis who have had incomplete mass regression. Therefore I think that prospective collection of data in a larger patient population is warranted before we can really draw firm conclusions.

Dr Adams. And, of course, we need to know better how that hypertension gets managed.

Dr Stulak. Absolutely.

Dr Adams. My last question is this: Given the detrimental effect of LVH on LV function, do you think we should incorporate LVMI in our future decision-making algorithms and guidelines? Specifically, in a patient with normal ventricular function, an ejection fraction of 70%, normal dimension, LV systolic dimension of 34 mm, and severe MR, would you regard a low or normal LVMI as an indication that watchful waiting rather than surgical intervention would be an appropriate strategy? In other words, are you going to counsel patients? I understand that if they have a high LVMI, you are going to say that they should have an operation, but would a completely normal LVMI maybe sway you toward watchful waiting?

Dr Stulak. Another great question. I do not think that LV mass rises to the same bar as ejection fraction and LV end-systolic dimension. Prior studies from our institution have documented excellent outcomes if the ejection fraction is normal and the LV end-systolic dimension is normal. I do not believe this study is designed to answer that question, but I do not think that a low LVMI would affect our decision to undertake surgical intervention in patients presenting early.

Dr Adams. John, congratulations.

Dr A. W. Atkinson (Raleigh, NC). I just want to touch on a point that Dr Adams made, and I think it was in your discussion about the confounding of hypertension. In particular, do you have any data on the postoperative management with afterload reduction until a return of normal LVMI?

Dr Stulak. That is an outstanding question, and this is certainly one of the limitations of this study. Although some patients are followed very aggressively at Mayo Clinic by the cardiologists, we do lose certain patients from distances to the community and their personal primary care physicians. Those followed at Mayo Clinic

are treated with an aggressive regimen of β -blockade and angiotensin-converting enzyme inhibition. I think to overcome this limitation, prospectively collected data and more accurate follow-up of hypertension control are crucial.

Dr Rakesh M. Suri (Rochester, Minn). John has done a fantastic job on this study. I just wanted to comment on Dr Adams' question. Of course, this is a very unique cohort of patients who all underwent early mitral valve surgery well within class I or class IIa guidelines, and as such, the findings are not surprising. They all have good late survival and a low incidence of late complications or stroke. The study was designed to characterize the change in LV mass following mitral valve repair and to understand factors influencing regression of ventricular hypertrophy. The separate question as to whether we can safely wait to allow LVH to develop cannot be addressed within the current study. Previous series have clearly demonstrated, however, that "watchful waiting" of patients severe MR once guideline-based surgical indications have been met, is associated with dire clinical consequences.

Dr Harold L. Lazar (Boston, Mass). I just want to follow up on the questions that Dr Adams raised about the pathophysiology for the mass regression. Did you look at the patients you actually excluded from the study, those with atrial fibrillation and coronary artery disease, to see whether there was a similar change in mass regression? In other words, does the presence of atrial fibrillation or coronary artery disease inhibit mass regression in patients who have valve repair for posterior leaflets?

Dr Stulak. That is an outstanding point, and we are currently actually looking at each different subset of those 2600 mitral valve repairs from all causes. Again, we wanted to start our investigation with a homogenous population, taking every possible confounding effect of cause out of the equation. Then, on interpreting our results, we were very enticed. Therefore we are going to extend this to larger groups of patients. You make a great point.