Impact of Left Ventricular Systolic Function on Outcome of Correction of Chronic Severe Aortic Valve Regurgitation: Implications for Timing of Surgical Intervention

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Background. **The timing of valve repair or replacement in patients with severe aortic valve regurgitation (AR) is controversial. We investigated the effect of left ventricular (LV) function on survival and recovery of LV performance and dimensions after correction of chronic severe AR.**

Methods. **We reviewed 530 consecutive patients who underwent aortic valve repair or replacement for severe AR between January 1, 2004, and June 30, 2014.**

Results. **The 30-day mortality was 0.75%. In multivariate analysis, older age (hazard ratio [HR] = 1.02, p = 0.03), preoperative LV ejection fraction (EF) <60% (HR = 1.78, p = 0.04), previous myocardial infarction (HR = 2.53, p = 0.01), and previous cardiac operation (HR = 1.82, p = 0.03) were associated with all-cause mortality. Ejection fraction was reduced before hospital discharge but then improved and was greater than preoperative levels at all subsequent intervals. The LV dimensions decreased early postoperatively and continued to decrease thereafter. In multivariate analysis, factors associated with LV dysfunction (EF <60%) 1 year after aortic valve replacement were preoperative LV end-systolic dimension ≥40 mm (odds ratio [OR] = 5.39, p < 0.01) and previous myocardial infarction (OR = 3.62, p = 0.04).**

Conclusions. **Preoperative LV dysfunction (EF <60%) had an adverse effect on overall survival after correction of chronic severe AR. Because survival is improved in patients with greater preoperative LVEF and because reverse LV remodeling is more complete with smaller LV dimensions, surgical intervention should be considered promptly in patients with chronic severe AR and deterioration of these indicators during echocardiographic surveillance.**

(Ann Thorac Surg 2016;■:■–■)

Severe aortic valve regurgitation (AR) leads to progressive left ventricular (LV) enlargement and dysfunction with time. Both low LV ejection fraction (EF) and large LV dimensions are associated with increased late mortality [1–3]. Thus, the American Heart Association / American College of Cardiology guidelines reflect the importance of prompt aortic valve replacement or repair for chronic severe AR in asymptomatic patients if there is decreased LVEF less than 50% (class I indication) [4]. As a class II recommendation, the guidelines suggest that aortic valve surgical repair is reasonable in asymptomatic patients with LVEF 50% or greater in the presence of an LV end-diastolic dimension (LVEDD) greater than 65 mm or LV end-systolic dimension (LVESD) greater than 50 mm.

Accepted for publication Aug 11, 2016.

Presented at the Fifty-second Annual Meeting of the Society of Thoracic Surgeons, Phoenix, AZ, Jan 23–27, 2016.

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The extent to which LV function and dimensions recover after correction of AR is unclear. Theoretically, LV size and function should recover to normal after correction of AR. With marked eccentric hypertrophy, however, variable degrees of myocardial fibrosis may develop, and in some patients, LV dysfunction progresses to an irreversible level, causing sustained postoperative LV dysfunction and enlargement, and late death.

In this study, we investigated the effect of LVEF on surgical outcomes after correction of severe AR. Further, we analyzed the recovery of LV function and dimensions after operation and sought to identify the clinical and echocardiographic predictors of long-term recovery in these indicators.

Material and Methods

This retrospective study was approved by the Mayo Clinic Institutional Review Board. We reviewed the medical records of adult patients (>18 years) who

Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.09.004

underwent aortic valve replacement or repair for chronic severe AR between January 1, 2004, and June 30, 2014. We included patients who had concomitant coronary artery bypass grafting, previous cardiac operations, aortic root replacement, ascending aorta replacement, or aortic arch replacement. We excluded patients who had moderate or less AR and those with acute AR resulting from aortic dissections or active endocarditis. Also excluded were patients with moderate or more aortic valve stenosis, subaortic stenosis, periprosthetic valve regurgitation, or primary diagnosis of ischemic or dilated cardiomyopathy. We did not include patients who underwent concomitant mitral valve repair or replacements, or LV assist device implantation. Five hundred thirty patients met the study's selection criteria.

Follow-up was ascertained by use of both the medical chart and a survey follow-up that was conducted 1, 3, 5, and 10 years postoperatively. The mean clinical follow-up period was 3.8 ± 3.2 years. Preoperative, predismissal, and follow-up transthoracic echocardiograms were reviewed. A follow-up echocardiogram was obtained in 278 of 526 survived patients (52.9%). A total of 1,124 follow-up echocardiograms were performed at a mean of 2.0 ± 2.8 years postoperatively and were categorized as predismissal, n = 505; 1 year or less, n = 235; 1 to 3 years, n = 174; 3 to 5 years, n = 121; and greater than 5 years, n = 89.

Echocardiographic studies were performed on commercially available ultrasound equipment in accordance with the American Society of Echocardiography guidelines [5]. In our laboratory, EF is measured by two-dimensional echocardiography with the use of the biplane Simpson's method. When calculated EF was not available, we used the cardiologist's reported visual estimate. The LV dimensions were measured by two-dimensional echocardiographic-guided M-mode.

Descriptive statistics for categoric variables are reported as frequency and percentage, and continuous variables are reported as mean (standard deviation) and median (range). Change of EF from preoperative time to a follow-up time point was tested by the signed rank test. The Kaplan-Meier method was used to draw survival curves and to calculate 5-year and 10-year survival statistics. Cox regression models were used to find the univariate and multivariate predictors of long-term mortality. In a preliminary analysis, the association between EF and the risk of overall mortality was explored as a p-spline function [6], adjusted for gender, preoperative New York Heart Association functional class, and presence or absence of coronary artery disease. As illustrated in Figure 1, the risk of death increased as preoperative LVEF declined below 60%, which supports the clinical decision of using 60% as the cutoff point. Linear regression was used to identify risk factors for EF below 60 at 1 year follow-up. The multivariable model considered univariately significant variables ($p < 0.05$) with model selection using the stepwise method. All statistical tests were two-sided, with the α level set at 0.05 for statistical significance.

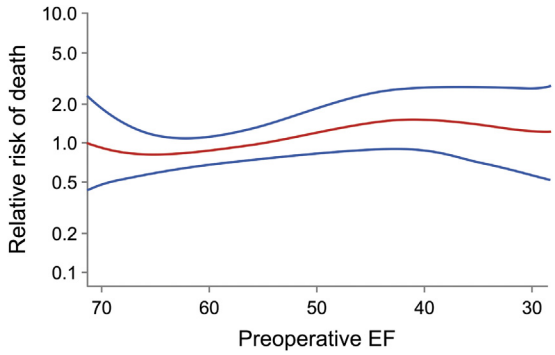

Fig 1. Association between preoperative left ventricular ejection fraction (EF) and the risk of overall mortality explored as a p-spline function. Dotted line indicates 95% confidence interval.

Results

Baseline Characteristics

The preoperative characteristics for all study patients are summarized in Table 1. The mean age was 57.1 ± 17.0 years. Approximately 80% of the patients were men. The mean preoperative LVEF was 56.1 ± 10.3%, and 298 patients (56.8%) had preoperative LVEF below 60%. One

Table 1. Baseline Patient Characteristics (N = 530)

Categoric Variables	n (%)
Age (y)	57.1 ± 17.0
Male sex	425 (80.2)
Hypertension	341 (64.3)
Diabetes	31 (5.8)
Dialysis	4 (0.8)
Severe chronic lung disease	3 (0.6)
Cerebrovascular disease	30 (5.7)
Previous cardiac operation	101 (19.1)
Previous myocardial infarction	29 (5.5)
Atrial fibrillation	53 (10.0)
LVEF (%)	56.1 ± 10.3
LVEDD (mm)	61.8 ± 7.9
LVESD (mm)	42.1 ± 8.3
RVSP (mm Hg)	34.6 ± 12.7
NYHA functional class	
I	161 (30.5)
II	197 (37.3)
III	146 (27.7)
IV	24 (4.5)
missing	2 (0.4)
Mitral regurgitation >mild	61 (11.7)
Tricuspid regurgitation >mild	50 (9.6)
Operative status	
Elective	499 (94.2)
Urgent	31 (5.8)

LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; NYHA = New York Heart Association; RVSP = right ventricular systolic pressure.

hundred one patients (19.1%) had a history of previous cardiac operations.

Operative Details

As seen in Table 2, 433 patients underwent aortic valve replacement and 97 patients underwent aortic valve repair. Valve-sparing root replacement with associated correction of AR was classified as an aortic repair. There were 206 mechanical valves implanted: CarboMedics (Sulzer CarboMedics, Austin, TX) (n = 148), St Jude Medical (St Jude Medical, St Paul, MN) (n = 53), and On-X valve (On-X Life Technologies, Austin, TX) (n = 5); and 227 patients received biologic valves: Carpentier-Edwards (Edwards Lifesciences, Irvine, CA) (n = 65), Mitroflow (Sorin Group USA, Arvada, CO) (n = 45), Trifecta (St Jude Medical) (n = 34), Biocor (St Jude Medical) (n = 20), Epic (St Jude Medical) (n = 9), Mosaic (Medtronic, Minneapolis, MN) (n = 8), Hancock (Medtronic) (n = 10), Freestyle (Medtronic) (n = 29), and aortic valve homografts (n = 7).

Early and Overall Mortality

There were four deaths during hospitalization or within 30 days postoperatively (0.75%). The 5-year and 10-year survival rates were 85.4% (confidence interval [CI] 81.7% to 89.2%) and 69.5% (CI 61.3% to 78.3%), respectively. As seen in the survivorship curves in Figure 2, patients who had preoperative LVEF below 60% had lower survival rate than those with LVEF of 60% or greater (log-rank, $p = 0.008$). In multivariate analysis, patient characteristics associated with all-cause mortality were older age (hazard ratio [HR] = 1.02, $p = 0.03$), preoperative LVEF below 60% (HR = 1.78, $p = 0.04$), previous myocardial infarction (HR = 2.53, $p = 0.01$), and previous cardiac operations (HR = 1.82, $p = 0.03$) (Table 3).

Changes in Long-Term Postoperative LVEF and LV Dimensions

The late changes in LVEF, LVEDD, and LVESD are shown in Figures 3, 4, and 5, respectively. Ejection fraction was reduced in echocardiograms obtained before hospital dismissal but then improved and was greater than the preoperative level at all subsequent intervals. An early decrease in LVEDD and LVESD occurred early postoperatively and was sustained thereafter.

Table 2. Operative Details (N = 530)

Factor	n (%)
Aortic valve replacement	433 (81.7)
Mechanical	206 (38.9)
Biologic	220 (41.5)
Homograft	7 (1.3)
Aortic valve repair	97 (18.3)
Concomitant procedures	
Aortic replacement (root, ascending, and/or arch)	178 (33.6)
CABG	95 (17.9)
Tricuspid repair or replacement	19 (3.6)
Postoperative IABP use	15 (2.8)
Cardiopulmonary bypass time (min)	106.2 ± 57.2
Aortic cross-clamp time (min)	78.4 ± 43.4

CABG = coronary artery bypass grafting; IABP = intraaortic balloon pumping.

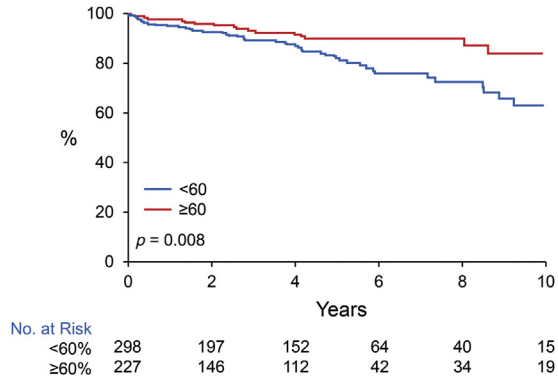

Fig 2. Overall survival after correction of severe aortic valve regurgitation stratified by preoperative left ventricular ejection fraction greater than or less than 60%.

Predictors of Sustained LV Dysfunction

Table 4 shows the analysis for predictors of LVEF below 60% 1 year after operation. In multivariate analysis, the variables associated with LVEF below 60% 1 year after operation were preoperative LVESD of 40 mm or greater (odds ratio [OR] = 5.39, $p < 0.01$), and previous myocardial infarction (OR = 3.62, $p = 0.04$).

Univariate Cox regression model was performed to investigate the effect of the changes of LVEF and LVEDD between discharge and 1 year after the operation on overall survival. Patients who had worse LVEF at 1 year compared with predismissal LVEF had a higher mortality rate (HR = 3.15, $p < 0.01$). Patients who had larger LVEDD at 1 year compared with predismissal LVEDD also had a higher mortality rate (HR = 1.09, $p = 0.03$). The early decline of LVEF from preoperative study to predismissal study was not predictive of late survival (HR = 0.71, $p = 0.20$).

Asymptomatic Patients

One hundred sixty-one patients (30.5%) were preoperatively asymptomatic (New York Heart Association class I). In this population, there was no 30-day mortality. The 5-year and 10-year survival rates were 91.1% (CI 85.7% to 96.6%) and 77.8% (CI 59.7% to 99.9%), respectively. The late survival rate was better than in symptomatic patients ($p = 0.01$).

Comment

In this study, we found that reduced preoperative LVEF (<60%) adversely affected overall survival after surgical correction of AR. This finding may expand the current guidelines, which recommend prompt operation in patients who have severe AR with LV dysfunction

Table 3. Predictors of Overall Death

	Univariate Cox Regression		Multivariate Cox Regression	
Variable	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age	1.03 (1.01–1.04)	<0.01	1.02 (1.00–1.04)	0.03
NYHA class III or IV	1.95 (1.21–3.14)	<0.01		
Previous myocardial infarction	3.31 (1.64–6.68)	<0.01	2.53 (1.22–5.25)	0.01
Concomitant CABG	1.76 (1.01–3.04)	0.05		
Atrial fibrillation	2.19 (1.08–4.42)	0.03		
Moderate or severe mitral regurgitation	1.89 (0.79–4.51)	0.15		
Aortic valve replacement	1.28 (0.65–2.50)	0.48		
Mechanical valve	0.63 (0.37–1.06)	0.08		
Preoperative LVEF <60%	2.11 (1.21–3.67)	<0.01	1.78 (1.01–3.14)	0.04
Preoperative LVEDD	0.97 (0.94–1.01)	0.12		
Preoperative LVESD	1.00 (0.97–1.04)	0.86		
Preoperative RVSP	1.02 (1.01–1.04)	0.01		
Previous cardiac operation	1.98 (1.17–3.37)	0.01	1.82 (1.06–3.14)	0.03
Aortic valve pressure gradient at dismissal	1.01 (0.97–1.05)	0.68		

CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; NYHA = New York Heart Association; RVSP = right ventricular systolic pressure.

(EF <50%) regardless of symptoms [4]. We previously reported that operative mortality for AVR in patients with AR was higher in those with markedly reduced LVEF than in those with moderately reduced or normal LVEF [7]. In that earlier series, operative mortality was 14% in the patients with LVEF below 35%. In the present study, 32 patients had LVEF less than 35%, and there was no 30-day mortality. Indeed, all operative mortality (0.75%) occurred in patients with preoperative LVEF above 50%. The reasons for decline in operative mortality in the recent era are multifactorial, reflecting improvements in surgical and anesthetic techniques, myocardial protection, prosthetic valve design, postoperative care, and concomitant medical therapy. Therefore, in the current era, aortic valve operations can be performed with very low early mortality even in patients with severe LV dysfunction if careful attention is given to the selection of patient and to intraoperative and postoperative care; however, reduced LVEF had a significant impact on overall long-term survival.

The current recommendations for the treatment of asymptomatic patients with chronic severe AR stipulate prompt surgical repair if LVEF is reduced to less than 50% [4, 8]. Our study indicates that the LVEF threshold for operation may be higher: 60%. Patients who had preoperative LVEF less than 60% had lower survival rate up to 10 years than did patients with greater preoperative EF, and those with preoperative LVEF less than 60% also had lower EF at each time point postoperatively. Indeed, patients who did not have improvement in LV function by 1 year after operation had a three-fold greater risk of subsequent overall death. These findings suggest that it is critically important to perform surgical intervention for patients with chronic severe AR before they experience

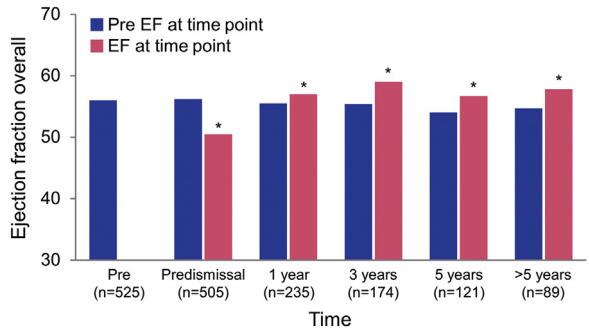

*Fig 3. Mean left ventricular ejection fraction (EF) before (Pre) and after correction of aortic valve regurgitation. Pink bars indicate the EF at each postoperative time point. Blue bars indicate the preoperative EF for the same patients whose postoperative EF data is available at that time point for purpose of paired comparison. *Statistically significant change in EF in the paired data.*

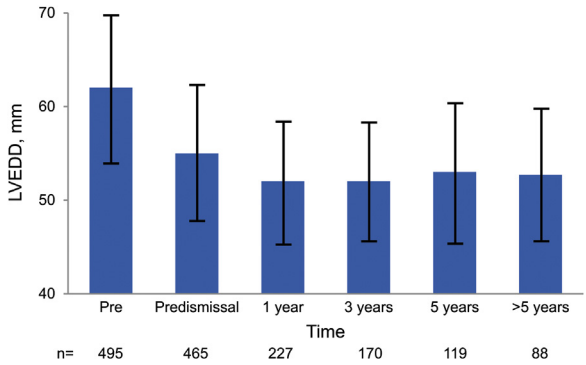

Fig 4. Left ventricular end-diastolic dimension (LVEDD) before (Pre) and after correction of aortic valve regurgitation. Mean ± standard deviation of LVEDD at each time point.

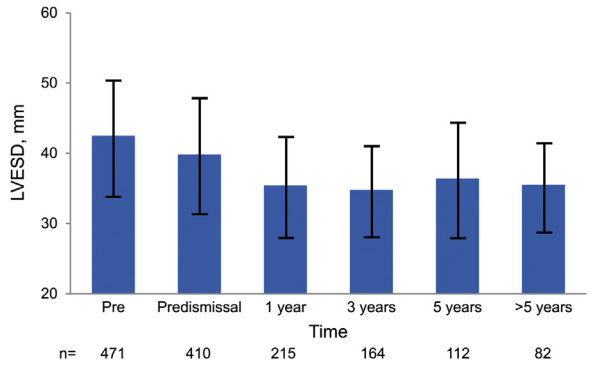

Fig 5. Left ventricular end-systolic dimension (LVESD) before (Pre) and after correction of aortic valve regurgitation. Mean ± standard deviation of LVESD at each time point.

LV dysfunction [9]. Early operations can be justified by good operative outcomes in asymptomatic patients. Our findings in the current study are consistent with available information on the impact of reduced ventricular function in patients undergoing correction of mitral valve regurgitation. In earlier studies, the hazard ratio for death after correction of chronic mitral valve regurgitation was 2.79 in patients with LVEF below 60% compared with those with greater EF [10].

There is controversy regarding the hemodynamic performance of aortic valve prostheses and the potential impact of valve selection on patient survival [11, 12]. In the current study, the 10-year survival among patients receiving mechanical prostheses was 75% compared with 57% for patients with bioprosthetic aortic valves. In multivariate analysis, valve type was not significantly associated with overall survival. Recovery of LV function was similar in patients with mechanical valves and patients with bioprostheses. We did not have sufficient numbers of patients to perform a subgroup analysis of different models and different indexed prosthetic valve areas.

An important goal of this study was to document changes in LV systolic function and size by echocardiography during follow-up after surgical correction of AR and to identify factors predictive of more complete recovery of normal EF (≥60%). Left ventricular reverse remodeling after correction of AR has not been well documented. In one study, Zhang and associates [13] reported that despite the correction of AR, the LVEDD remained abnormal in more than one third of patients, and this was associated with low preoperative EF. We found that after an initial decline from the preoperative study to the study performed before to hospital dismissal, mean EF increased and was significantly greater than preoperative levels at all subsequent intervals. Regression in LV diastolic dimensions occurred early after operation and through the first year postoperatively; LV diastolic dimension remained stable thereafter. These findings are consistent with the report of Scognamiglio and colleagues [14], although those authors did not have information on LVEF at hospital dismissal.

The mechanism of initial decline of LVEF after correction of AR appears to be similar to the fall in LVEF early after correction of mitral valve regurgitation [15]. The recovery of LV function after correction of mitral valve regurgitation was reported by Suri and colleagues [16], and in that study, we found that LVEF declines initially after correction of mitral valve regurgitation but that LVEF improves steadily over time. These data are consistent with the findings in our current study. However, after correction of mitral valve regurgitation, mean LVEF was still lower during follow-up compared with preoperative values, whereas mean EF increased to levels greater than preoperative values after correction of AR. It should be noted that there were differences in preoperative EF: 62% for patients with mitral valve regurgitation versus 56% in the current study of patients with chronic

Table 4. Predictors of Ejection Fraction Less Than 60% 1 Year After Operation

	Univariate Logistic Regression		Multivariate Logistic Regression	
Variable	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age	1.01 (1.00–1.03)	0.19		
NYHA class III or IV	1.73 (0.99–3.01)	0.06		
Previous myocardial infarction	3.68 (1.18–11.45)	0.02	3.62 (1.04–12.68)	0.04
Concomitant CABG	1.15 (0.60–2.21)	0.68		
Atrial fibrillation	1.44 (0.60–3.48)	0.41		
Aortic valve replacement	1.47 (0.73–2.95)	0.28		
Mechanical valve replacement	0.96 (0.55–1.69)	0.89		
Preoperative LVEF <60%	3.22 (1.87–5.53)	<0.01		
Preoperative LVEDD ≥65mm	2.97 (1.61–5.48)	<0.01		
Preoperative LVESD >40mm	5.16 (2.85–9.32)	<0.01	5.39 (2.95–9.86)	<0.01
Preoperative RVSP	1.01 (0.98–1.03)	0.58		
Aortic valve pressure gradient at dismissal	0.97 (0.94–1.01)	0.11		

CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; NYHA = New York Heart Association; RVSP = right ventricular systolic pressure.

aortic valve regurgitation. Differences in the course of LV remodeling in patients with corrected aortic versus mitral regurgitation may also relate to loading conditions before valve repair or replacement. In aortic regurgitation, there is both an increased afterload and an increased preload, whereas in mitral regurgitation, the afterload is actually decreased.

The identification of predictors of recovery of normal EF is important because the prognosis associated with LV dysfunction after operation is poor. Multivariate analysis demonstrated that the risk factors for persistently abnormal EF (<60%) 1 year after operation were preoperative LV end-systolic diameter 40 mm or greater and previous myocardial infarction. The current guidelines for the treatment of asymptomatic patients with chronic severe AR suggest prompt operation if LVESD becomes greater than 50 mm. Our study indicates that the LVESD threshold for operation can be lower than the current guideline.

This study has the usual limitations of a retrospective analysis, including selection and reporting biases. Additional limitations included these: (1) clinical and echocardiographic follow-up could not be obtained in all patients, (2) follow-up period was limited, and (3) advancement in surgical devices, techniques, and postoperative care occurred throughout the study period. With longer follow-up, structural valve deterioration in prosthetic aortic valves and recurrent aortic regurgitation in the repair group might be an issue influencing patients' survival and LV function.

In conclusion, preoperative LV dysfunction (EF <60%) has an adverse effect on late survival after correction of chronic severe AR, and intervention should be considered when EF falls below this threshold. LVEF declines in the early postoperative period after correction of AR and improves over time. Because LV function is more likely to normalize in patients with greater EF and smaller dimensions, operation should be considered promptly in those with chronic severe AR and with deterioration of these indicators during echocardiographic surveillance.

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DISCUSSION

DR JUAN A. CRESTANELLO (Columbus, OH): I would like you to elaborate a little bit about the change on the guidelines criteria. Currently the recommendation is for asymptomatic patients who have severe aortic regurgitation and left ventricular EF below 50% or an increase of the left ventricular dimensions above 50 mm for the end-systolic diameter or above 65 mm for diastolic diameter to undergo surgical repair. Based on these findings, how would you modify the guidelines?

DR MURASHITA: Based on the findings in this study, we can suggest that surgical repair should be done when patient's EF is reduced below 60%, and in terms of left ventricular systolic diameter, we think the threshold for surgical repair can go up to 40 mm.

DR LARRY STEPT (Pittsburgh, PA): On your graphs you showed in both the cohorts of above 60% and below 60% EF after the

initial dropoff of an EF in the predischarge echocardiogram that both groups showed an increase in EF and a decrease in end-diastolic volume over time. If both groups, the groups above 60% and below 60%, are showing increases in EF and decreases in diastolic diameter, what theories do you have as to why the group with below 60% EF initially has a higher long-term mortality?

DR MURASHITA: You mean short-term mortality or long-term?

DR STEPT: I think your study shows that late mortality is greater in the group that initially had below 60% EF who were operated on, but both groups show an increase in EF and a decrease in diastolic volume over time after their operations. Why do you think that the group that initially had the EF below 60% has a higher long-term mortality than the group that initially had an EF above 60%?

DR MURASHITA: Our data showed that patients with EF below 60% 1 year after their operations had a higher mortality rate, and our data showed that an early decline in EF did not have impact on late survival. I think the key point in terms of overall survival is preoperative LV function and how much recovery the patients get after surgical correction for AR.

DR STEPT: Let me ask it a different way. In the group that had initially an EF above 60% compared with the group that had below 60% initially, was the rate of recovery or the increase in EF after the operation greater in the group that initially had better ventricular function compared with the group that had lesser ventricular function? Did you break that down in terms of how much more recovery they had in their ejection fraction?

DR MURASHITA: The mean EF in the follow-up period is about the same with both groups, about 55% of EF. So I would say the recovery of EF is greater than in patients with a lower EF.

DR STEPT: So if the recovery is greater in the initial group that had a lower EF, why do you think that their mortality long term is greater?

DR MURASHITA: It is a hard question to answer. This should be analyzed further in the future.