Diastolic Function Predicts Outcome after Aortic Valve Replacement in Patients with Chronic Severe Aortic Regurgitation

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ABSTRACT

Background: Due to eccentric hypertrophy and fibrosis, patients with severe aortic regurgitation (AR) have diastolic dysfunction. Increased fibrosis correlates with increased myocardial stiffness and worsening of diastolic function. Patients with irreversible left ventricular (LV) dysfunction have severe myocardial fibrosis and myocyte apoptosis and do not benefit from aortic valve replacement (AVR).

Hypothesis: To investigate whether diastolic properties of LV predicts outcome after AVR in patients with chronic severe AR and LV systolic dysfunction.

Methods: The study population consisted of 41 patients with chronic severe AR and LV systolic dysfunction. Preoperative echocardiographic examinations were repeated at the postoperative 6th month. Left ventricular ejection fraction (LVEF) was calculated. Diastolic function was evaluated with Doppler echocardiography. Patients were classified as Group 1 (impaired relaxation), Group 2 (pseudonormalization), and Group 3 (restrictive pattern).

Results: Postoperative LVEF was significantly increased in Group 1, whereas it tended to decrease in Group 3. Left ventricular size was significantly decreased in Group 1 and 2 during the postoperative period. Multivariate linear regression analysis showed that deceleration time and early/late ratio were independent predictors of postoperative changes in LVEF.

Conclusions: Assessment of diastolic function is a reliable parameter in predicting outcome of AVR in patients with chronic AR and systolic dysfunction.

Introduction

Myocardial fibrosis and myocyte degeneration/necrosis are common in patients with chronic severe aortic regurgitation (AR). Myocardial fibrosis and apoptosis increase with the progression of the disease, lead to progressive chamber dilatation, and irreversible left ventricular (LV) dysfunction.^{1,2} Left ventricular systolic dysfunction is initially reversible with surgery. Current guidelines recommend aortic valve replacement (AVR) for patients with severe AR and LV dysfunction.^{3,4} However, AVR should be performed before onset of irreversible LV dysfunction. Patients who have irreversible LV dysfunction do not benefit from AVR.^{5,6,7} However, preoperative identification of these patients is very difficult.^{7–10}

Due to eccentric hypertrophy and myocardial fibrosis, patients with severe AR usually have diastolic dysfunction. Increased myocardial fibrosis correlates with the worsening of diastolic function.^{2,11,12}

The aim of the study was to investigate whether diastolic properties of LV predicts outcome after AVR in patients with chronic severe AR and LV systolic dysfunction.

Methods

Subjects

The study population consisted of 41 patients with chronic severe AR and LV systolic dysfunction (18 women and 23 men; mean age: 44.4±11.7 years). Patients with atrial fibrillation or flutter, evidence of coronary artery disease, aortic stenosis, mitral stenosis, and severe mitral regurgitation were excluded. Due to poor image quality, patients with posteriorly directed regurgitant jet were also excluded from study. Informed consent was obtained from all subjects and the Local Ethical Committee approved the study.

Echocardiographic Examinations

All echocardiographic examinations were performed with an Acuson Sequoia C 256 machine (Acuson Corporation, Mountain View, Calif., USA). Echocardiographic techniques and calculations were performed in accordance with the recommendations of the American Society of Echocardiography.¹³ Left ventricular ejection fraction (LVEF) was calculated by using a modified Simpson's method. The grading of AR severity was based on a number of echocardiographic and

Doppler parameters as previously described.¹⁴ Echocardiographic examinations were performed in all patients in the preoperative period and repeated during the postoperative 6th month.

Transmitral flow was recorded by pulsed wave Doppler placed between the mitral leaflet tips in an apical 4-chamber view. Peak transmitral early (E) and late (A) diastolic flow velocities and deceleration time (DT) were measured.

Tissue Doppler imaging was performed in the apical 4-chamber view and pulsed wave sample volume was placed in lateral mitral annulus. Peak annular systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities were recorded.

Diastolic function was classified as normal ($E/A > 1$, $DT < 220$ ms, and $Ea/Aa > 1$), impaired relaxation ($E/A < 1$, $DT > 220$ ms, and $Ea/Aa < 1$), pseudonormalization ($E/A = 1-2$, $DT = 150-200$ ms, and $Ea/Aa < 1$), and restrictive pattern ($E/A > 2$ or $DT < 150$ ms and $Ea/Aa < 1$).¹⁵ Patients were divided into 3 groups: Group 1 (impaired relaxation), Group 2 (pseudonormalization), and Group 3 (restrictive pattern).

Interobserver Variability

Left ventricular diameters, LVEF, E and A velocities, DT, Sa, Ea, and Aa velocities were measured by two independent observers. Interobserver variability was assessed by calculating the coefficient of variation. The coefficient of variation was $< 5\%$ for all measurements. Any discrepancy was resolved by consensus.

Statistical Analysis

All calculations were performed with the Statistical Package for the Social Sciences 11.5 (SPSS 11.5) program. Levene's test was used for assessment of homogeneity of variances. Differences in mean values of continuous variables were tested by using one-way analysis of variance (ANOVA) with Tukey post hoc test assuming equal variances and Games-Howell post hoc test assuming nonequal variances between the groups. Categorical variables were tested with the χ^2 test. Preoperative and postoperative echocardiographic variables were compared with the Friedman test and in case of significance, with the Wilcoxon test. The Pearson correlation analysis was used to establish the association between preoperative variables and the postoperative change in LVEF (Δ LVEF). The association between preoperative data and the magnitude of Δ LVEF was tested by linear regression analysis.

Results

The etiology of AR had been considered to be rheumatic in 38 patients and a bicuspid aortic valve in 3 patients. All patients were in New York Heart Association classes I or II. Impaired relaxation, pseudonormalization, and restrictive pattern had been detected in 17, 13, and 11 patients, respectively. Four patients in Group 1, 13 patients in Group

2, and 8 patients in Group 3 had S4 on physical examination. S3 gallop was heard in 4 patients of Group 3. No patient had clinical evidence of circulatory congestion.

Five patients (1 in Group 1, 2 in Group 2, and 2 in Group 3) refused surgery. The mean follow-up interval was 6.2 ± 1.7 mo. After surgery, 3 patients in Group 3 died due to left ventricular dysfunction at postoperative first, second, and 10th days.

Comparison of the Groups

The mean age was similar between the groups. End-diastolic diameter, end-systolic diameter, end-diastolic volume, end-systolic volume, and left atrial (LA) diameter were progressively increasing, while LVEF was decreasing from Group 1 to Group 3. Tissue Doppler parameters (Sa, Ea, and Aa wave velocities) were similar in Group 1 and 2 and was significantly higher than in Group 3 (Table 1).

At the postoperative 6th month, LVEF was significantly increased in Group 2 ($p < 0.001$) and slightly increased in Group 2 ($p = 0.08$), whereas it tended to decrease in Group 3 ($p = 0.2$) (Table 2, Figure 1). Δ LVEF was significantly higher in Group 1 ($p < 0.001$). Postoperative LVEF was increased in 16 (100%) and 8 (72.7%) patients of Group 1 and Group 2, respectively. However, postoperative LVEF was not increased in any of the patients in Group 3. Both end-diastolic and end-systolic diameters were significantly decreased in

Figure 1. Graph shows changes of ejection fraction with aortic valve replacement in groups. Postoperative ejection fraction was significantly increased in Group 1 and slightly increased in Group 2, whereas it tended to decrease in Group 3. Abbreviation: EF = left ventricular ejection fraction.

Table 1. Comparison of demographic and preoperative echocardiographic variables among the patients groups

	Group 1 (n = 17)	Group 2 (n = 13)	p1 Group 1 versus Group 2	Group 3 (n = 11)	p2 Group 1 versus Group 3	p3 Group 2 versus Group 3
Age	44.9±13.6	43.0±11.2	0.7	45.2±9.6	0.9	0.6
EDD, mm	66.2±7.4	68.8±6.4	0.1	70.5±5.8	0.01	0.3
ESD, mm	53.3±3.7	57.5±4.1	0.006	60.2±4.0	<0.001	0.1
EDV, mL	225.6±26.0	247.7±34.5	0.07	263.9±36.9	0.004	0.2
ESV, mL	137.7±21.8	165.4±26.8	0.007	184.6±32.2	<0.001	0.09
LVEF, %	39.1±5.2	33.6±3.5	0.001	30.5±2.7	<0.001	0.08
LAD, mm	42.8±3.2	45.7±4.0	0.07	48.6±5.9	0.001	0.1
E/A ratio	0.72±0.25	1.66±0.12	<0.001	2.47±0.45	<0.001	<0.001
DT, ms	247.1±16.2	175.3±24.5	<0.001	128.0±12.9	<0.001	<0.001
Sa, cm/s	12.5±3.0	12.0±1.7	0.6	8.8±2.1	<0.001	0.002
Ea, cm/s	16.7±6.3	18.0±3.3	0.5	11.9±4.9	0.02	0.006
Aa, cm/s	14.4±4.7	18.4±4.6	0.2	10.9±2.2	0.001	<0.001

Abbreviations: Aa = peak annular late diastolic velocity; DT = deceleration time; Ea = peak annular early diastolic velocity; EDD = end-diastolic diameter; EDV = end-diastolic volume; ESD = end-systolic diameter; ESV = end-systolic volume; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; Sa = peak annular systolic velocity.

Group 1 and 2. But, there was an insignificant reduction in end-diastolic and end-systolic diameters in Group 3.

Preoperative Echocardiographic Predictors of the Postoperative Changes in LVEF

Preoperative LVEF, end-systolic diameter, Sa, E velocity, E/A ratio, and DT were univariately associated with Δ LVEF (Figure 2, Table 3). But multivariate linear regression

analysis showed that only DT ($p < 0.001$) and E/A ratio ($p = 0.02$) were independent predictors of Δ LVEF.

Discussion

In this prospective study, we found that patients with mild or moderate diastolic dysfunction derived more benefit from AVR compared with patients with advanced diastolic

Figure 2. Postoperative changes of left ventricular ejection fraction (Δ LVEF) was positively correlated with deceleration time and negatively correlated with E/A ratio. Scatter plot of linear correlation and 95% confidence interval are shown. **Abbreviation:** EF = left ventricular ejection fraction; LV = left ventricle; E/A = early/late; LVEF = postoperative change in left ventricular ejection fraction.

Table 2. Postoperative changes in left ventricular diameters and LVEF

	Group 1 (n = 16)*	Group 2 (n = 11)**	Group 3 (n = 6)***
LVEF (%)			
Preoperative	39.1±5.3	33.3±3.1	31.5±2.5
Postoperative	49.8±6.0	38.4±5.7	27.8±3.4
ΔLVEF (%)	+10.9±2.4	+5.2±5.9	-3.7±3.2
p	<0.001	0.08	0.2
End-diastolic diameter (mm)			
Preoperative	66.0±4.4	68.6±5.4	69.9±5.2
Postoperative	53.2±5.9	58.7±4.4	66.3±3.7
ΔEDD	12.8±6.1	9.9±4.1	3.6±3.4
p	<0.001	0.003	0.09
End-systolic diameter (mm)			
Preoperative	53.3±3.7	57.5±4.1	60.2±4.0
Postoperative	39.5±4.7	46.8±5.8	57.5±2.3
ΔESD	13.6±4.9	10.7±4.7	1.9±3.5
p	<0.001	0.003	0.2
*1 patient refused surgery **2 patients refused surgery ***2 patients refused surgery and 3 patients died before sixth mo control. Abbreviations: ΔEDD = postoperative change in end-diastolic diameter; ΔESD = postoperative change in end-systolic diameter; LVEF = left ventricular ejection fraction; ΔLVEF = postoperative change in left ventricular ejection fraction.			

dysfunction. It has been reported that asymptomatic patients with AR and normal LVEF have an excellent prognosis. The annual mortality rate is less than 0.5%. However, AR is a progressive disease and LV dysfunction develops in 4%–6% of patients per year.¹⁶ Nonoperative management of patients with LV dysfunction is associated with high mortality.¹⁰ It is also known that preoperative LVEF is one of the most important predictors of adverse outcome after AVR in patients with severe AR.^{17,18,19} However, recent studies showed that aortic valve surgery may reduce LV volumes and increase LVEF in patients with LV systolic dysfunction.^{3,10,17,20} Current guidelines recommend AVR for patients with severe AR and LV systolic dysfunction.^{3,4} But, the threshold of LVEF for functional recovery has not been defined. Furthermore, progressive LV dilatation and LV functional impairment may continue despite successful AVR in a subset of patients, implying that there is irreversible myocardial dysfunction.^{7,10,17} In our study, LV systolic function was impaired in 9 of 33 patients at 6 mo after successful AVR. AVR should be performed before developing irreversible LV dysfunction. However, preoperative identification of these patients is very difficult.^{7,8,10}

Myocardial fibrosis and myocyte degeneration/necrosis are common in patients with chronic, severe AR. With the progression of the disease, myocardial fibrosis and

myocyte apoptosis increase and may lead to progressive chamber dilatation, irreversible LV dysfunction, congestive heart failure, and death.^{1,2,12} Increased myocardial fibrosis also correlates with worsening of diastolic function.^{12,21,22} In

Table 3. Variables that are univariately associated with postoperative changes in LVEF

	R ²	p
Preoperative LVEF, %	0.37	0.01
Preoperative end-systolic diameter, mm	-0.28	0.02
Sa, cm/s	0.33	0.001
E, cm/s	-0.38	0.002
E/A ratio	-0.62	<0.001
Deceleration time, ms	0.75	<0.001

Abbreviations: E = peak transmitral early diastolic flow velocity; LV = left ventricle; LVEF = left ventricular ejection fraction; ΔLVEF = postoperative change in left ventricular ejection fraction; Sa = peak annular systolic velocity.

our study all patients had diastolic dysfunction at different levels. Patients with restrictive pattern had the lowest LVEF and largest chamber size. The relation between diastolic function assessed with echocardiography and outcome of surgery has not been researched previously. In our study, LVEF was improved in all of Group 1 patients and 72.7% of Group 2 patients, whereas it was not improved in Group 3 patients after AVR. Furthermore, linear regression analysis showed that DT and E/A ratios were independent predictors of changes of postoperative LV systolic function. It is known that DT is the best noninvasive marker of ventricular chamber stiffness.²³ We also showed that restrictive pattern was associated with poor outcome of surgery and may represent irreversible LV dysfunction. On the basis of these findings, we recommend that AVR should be offered to patients with LV systolic dysfunction and impaired relaxation or pseudonormalization. Alternative treatment methods such as vasodilator therapy or cardiac transplantation rather than AVR may be recommended to patients with LV systolic dysfunction and restrictive pattern.

Study Limitations

Our study included a relatively small number of patients, but it is difficult in one center to be presented with many patients with chronic severe AR and LV systolic dysfunction. Our results must be confirmed with further studies.

Conclusions

Patients with mild diastolic dysfunction derived more benefit from AVR than patients with advanced diastolic dysfunction. Deceleration time and E/A ratio are independent predictors of postoperative improvement in LVEF in patients with severe AR and LV systolic dysfunction. Assessment of diastolic function with Doppler echocardiography is a noninvasive, simple, and reliable preoperative parameter in predicting outcome of surgery and may help in the determination of treatment in patients with chronic, severe AR and LV systolic dysfunction.

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