Preoperative factors for early recovery of left ventricular function after aortic valve replacement for chronic aortic regurgitation

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Preoperative factors for early recovery of left ventricular function after aortic valve replacement for chronic aortic regurgitation

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ABSTRACT

Preoperative factors for early recovery of left ventricular function after aortic valve replacement for chronic aortic regurgitation

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Aortic valve replacement improves left ventricular(LV) systolic function in patients with chronic aortic regurgitation. Our objective was to determine predictors for normalization of impaired LV systolic function after valve replacement for chronic aortic regurgitation.

Between 1997 and 2007, 171 patients underwent aortic valve replacement for severe chronic aortic regurgitation. Of these patients, we examined 79 patients with LV systolic dysfunction or severe LV dilatation preoperatively, who were evaluated by echocardiography at predischarge and early follow-up (mean, 6 months). Mean preoperative ejection fraction was 49%. Mean LV end-systolic and end-diastolic dimensions were 52.3±8.4 mm and 69.6±7.8 mm, respectively. In the early follow-up, 62 of 79 patients exhibited restored normal LV function. LV end-systolic dimension and LV end-diastolic dimension were significantly decreased early after aortic valve replacement (52.3±8.4mm vs. 37.8±6.9mm, and 69.6±7.8mm vs. 51.6±6.4mm, respectively). Operative mortality was 3.7%. Multivariate stepwise regression analysis revealed that preoperative indexed LV end-systolic dimension was independent predictors of restored LV systolic function. The sensitivity and specificity in predicting normalization of LV function were 88% and 92% for indexed LVESD <35.3mm/㎡ and 71% and 86% for indexed LVEDD <44.4mm/㎡.

In patients who received a valve replacement for chronic aortic regurgitation, smaller indexed LV systolic dimension was associated with early restoration of LV systolic function .

Key words : Aortic valve replacement, Chronic aortic regurgitation, Ventricular function

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I. INTRODUCTION

Aortic regurgitation (AR) causes both volume overload and pressure overload.[1] As the disease progresses, preload reserve and compensatory hypertrophy permit the ventricle to maintain normal ejection performance with an increase in dimension and wall thickness despite the elevated afterload (called afterload mismatch). Most of these patients are asymptomatic and have an excellent prognosis.[2]

In many patients, however, the balance between afterload excess, preload reserve, and hypertrophy cannot be maintained indefinitely; afterload mismatch, depressed contractility, or severe dilated left ventricular(LV) dimension ultimately results in reduced ejection fraction(EF).[2-4] The standard of care is to monitor patients with chronic severe AR carefully and operate at the first sign of symptoms or LV dysfunction.[1-2,5] At this stage, surgical correction of AR can normalize or markedly improve LV systolic function.

Although the hemodynamic rationale for its correction can readily be appreciated in patients with a significantly dilated ventricle and impaired systolic function, surgery sometimes results in persistent LV dilatation and systolic dysfunction.[6-9] The physiologic changes in the left ventricle after valve replacement are incompletely understood [6], but the resulting systolic functional disturbances have important implications for morbidity and mortality before and after aortic valve replacement (AVR).[1, 3, 10]

In the present study, we evaluated several predictors for early recovery of LV function following AVR in patients with isolated, severe AR combined with LV systolic dysfunction.

II. MATERIALS AND METHODS

From 1997 to 2007, one-hundred and seventy-one patients underwent primary isolated AVR for chronic aortic regurgitation (at least 6 months' duration) at the Severance Cardiovascular Center of Yonsei University Health System in Korea. Acute AR such as aortic dissection and acute endocarditis, combined aortic stenosis, previous aortic valve surgery, concomitant coronary artery bypass graft, previous or associated mitral valve replacement or repair, and congenital disease unrelated to AR were excluded.

Of these 171 patients, the study group consisted of 79 patients with preoperative LV systolic dysfunction or severe LV dilatation, comprising 47% of our 171 experiences with AVR for chronic aortic regurgitation(Table 1).

Preoperative LV systolic dysfunction was defined as EF <50%. Preoperative severe enlarged LV was defined as left ventricular end-diastolic dimension (LVEDD) ≥70 mm and left ventricular end-systolic dimension (LVESD)≥50 mm. In 30 of the 79 patients, EF was 50-60%, but LV dimension was severely enlarged, and included in this study.

Patients included 54 men (68%) and 25 women (32%) with a mean age of 49.0±14.8 years. The mean BSA was 1.69±0.20m^2. Twenty patients (25%) and six patients (8%) had class III and IV heart failure, respectively, according to the New York Heart Association (NYHA) functional classification system. The etiologies of AR were congenital anomaly in 20 patients, rheumatic AR in 16, degeneration in 15, annulo-aortic ectasia in 12, and old infective endocarditis in 11. Preoperative variables are shown in Table 1.

Table 1. Preoperative clinical and echocardiographic characteristics of study patients

	Preoperative LV function		
	preserved	decreased	p
Number	92	79	
Age (yr)	63±13	49±15	<.001
LVEF (%)	60±10	49±10	<.001
LVESD (mm)	45.5±7.7	52.3±8.4	<.001
LVEDD (mm)	62.8±6.0	69.6±7.8	<.001

Patients with preoperative decreased LV function

	N = 79	%
Male	54	69
NYHA		
I	20	25
II	33	42
III	20	25
IV	6	8
Etiology of AR		
Congenital	20	25
Bicuspid	19	
Quadricuspid	1	
Rheumatic	16	20
Degenerative	15	19
Aneurysm / Annular dilatation	12	15
Old infective endocarditis	11	15
Aortitis	5	6
Ejection Fraction (%)		
<25	9	12
25< <50	40	50
50< <60	30	38

BSA , Body Surface Area ; NYHA, New York Heart Association

All patients had been treated with angiotensin-converting enzyme (ACE) inhibitors and other medications for heart failure prior to the operation. Hypothermic cardiopulmonary bypass and intermittent antegrade direct cold blood cardioplegia were used routinely for the surgical procedure.

69 of the patients (87%) received mechanical valves; 70 (89%) of patients had isolated AVR; 9 (13%) of patients underwent concomitant replacement of the ascending aorta (Table 2).

Table 2. Operative procedures of study patients

Procedure	N=79	%
Mechanical	69	87
Bioprosthesis	10	13
AVR only	70	88
Composite AVR and ascendina aorta replacement	7	9
Separate AVR and ascending aorta replacement	2	3

Echocardiography was performed within 1 month before surgery, during the immediate postoperative period (7 days after AVR), at early follow-up (the mean and median of follow-up time are both 6 months), and at late follow-up appointments. Normalization of LV systolic function was defined as EF > 50%. Regular follow-up was conducted at an outpatient clinic or by annual telephone call; follow-up was terminated at the end of 2007. The study was approved by the Institutional Review Board of Yonsei University College of Medicine.

Echocardiographic chamber quantification

Echocardiographic assessment was made using commercially available equipment with Doppler echocardiography according to a standard protocol. Interventricular septal wall thickness and LV internal dimensions at both end-diastole and end-systole were measured from M-mode Echocardiogram at the parasternal short-axis window. LV end-diastolic volume (EDV) and end-systolic volume (ESV) were measured by the biplane method of disks using 2D images from the apical 4- and 2-chamber views. Ejection fraction was calculated by M-mode or modified Simpson's rule. The left atrial (LA) diameter was measured at the end of ventricular systole from both the parasternal long-axis and the apical 4-chamber views.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation (SD). Cumulative survival was estimated by the Kaplan–Meier method using the date of surgery and date of the most recent follow-up. Differences in survival rates were determined by log-rank analysis. The paired *t*-test was used to compare two groups, while ANOVA and Tukey's multiple comparison test can do more than two groups. A multivariable analysis of independent factors was performed by stepwise regression. For continuous variables, diagnostic cut-off values with the most favorable sensitivities and specificities were identified by receiver operating characteristics curve analysis. Statistical significance was defined as a two-tailed P-value<0.05. SPSS for Windows, Release 15.0 (SPSS Inc., Chicago, IL) was used for statistical analysis.

III. RESULTS

Among the 171 patients who underwent AVR at our hospital, operative mortality was 2.9% (5/171), and overall survival was 89.8%, whereas operative mortality of the 79 patients with preoperative LV systolic dysfunction or severe LV dilatation in the present study was 3.7% (3/79), and overall survival was 86.9%. However, there was no significant difference in overall survival (operative and late deaths combined) between the 79 patients of our study group and the 92 patients with preserved LV function and LV dimension (Figure 1).

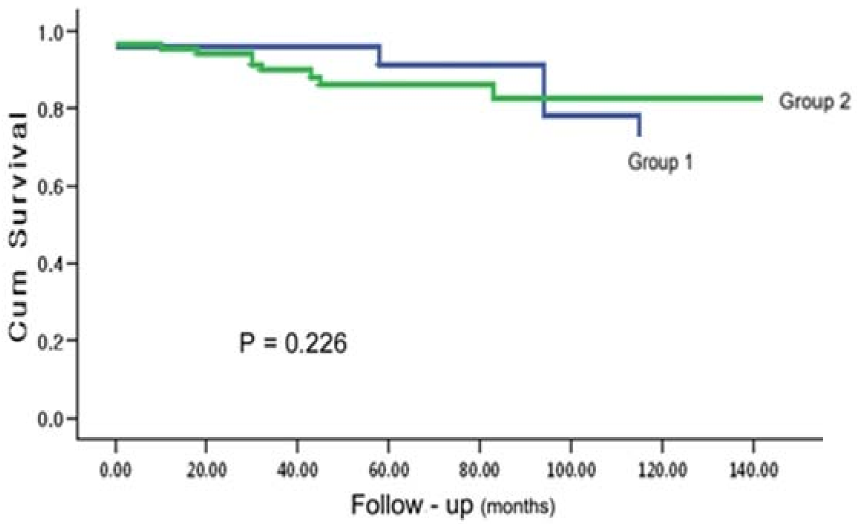

Figure 1. Comparison of cumulative survival at 10 years. Group 1 , 92 Patients with preserved LV function ; Group 2, 79 Patients with decreased LV function

In a multivariate analysis using the **Cox regression model, no variables were found to be independent predictors of operative mortality and overall survival.**

Table 3 shows the variables before and after the operation. Before the procedure, the mean preoperative ejection fraction was 49 ± 10%, mean LVESD was 52.3 ± 8.4 mm, and mean LVEDD was 69.6 ± 7.8 mm. In the immediate postoperative period, mean EF and LV dimensions were decreased. Early postoperative follow-up echocardiography (median, 6 months; mean, 6.4 ± 2.0 months) showed that mean EF increased from 49 to 55%. LVESD and LVEDD were significantly decreased after AVR (52.3 ± 8.4 mm vs. 37.8 ± 6.9 mm, 69.6 ± 7.8 mm vs. 51.6 ± 6.4 mm, respectively). At all time points, the mean EFs and LV dimensions were significantly different, according to analysis of variance (ANOVA) and Tukey's multiple comparison test. 62 of the 79 patients (78%) achieved normal LV systolic function in the early postoperative period. Late follow-up echocardiography (median, 35 months; mean 45 months; range, 12 months to 10 years) showed that LV systolic function was not restored in 7 of the remaining 17 patients (41%).

Table 3. Preoperative and postoperative echocardiographic parameters

	Preoperative	Immediate postoperative	Early postoperative	p
LVEF (%)	49 ± 10	43 ± 13	55 ± 11	<.001
LVESD (mm)	52.3±8.4	44.5±8.8	37.8±6.9	<.001
Indexed LVESD (mm/m^2)	31.2±6.1	26.8±6.4	22.4±5.8	<.001
LVEDD (mm)	69.6±7.8	56.4±7.5	51.6±6.4	<.001
Indexed LVEDD (mm/m^2)	41.5±6.2	33.4±5.9	30.8±4.9	<.001

LVEF, Left Ventricular Ejection Fraction ; LVESD, Left Ventricular End-Systolic Dimension ; LVEDD, Left Ventricular End-Diastolic Dimension ; Indexed LV dimension , LV dimension/BSA.
Comparison of three group by ANOVA and Tukey's multiple comparison test
Preoperative, within 1 month before surgery ; Immediate postoperative, 7 days after AVR ; Early postoperative, 6 months(mean, median) after AVR.

Univariate risk analysis demonstrated that NYHA functional classes, preoperative EF, LV dimensions, smaller indexed LV dimensions, and left atrial volume index were significant risk factors for early recovery of LV function after AVR. The immediate postoperative change in LVEF was not predictive of normal EF during the early preoperative period. Multivariate stepwise regression analysis showed that preoperative indexed LVESD was significant predictors (odds ratios ,7.60 ; 95% confidence interval, 1.51 to 15.11; p = 0.0095) (Table 4).

Table 4. Clinical and preoperative echocardiographic predictors for early recovery of LV function

	Univariate	Multivariate OR	95% Confidence Interval	*p* Value
Age	0.440			
Sex	0.823			
NYHA Class	0.001			
Preoperative EF	<0.001	1.28	(0.92 , 1.77)	0.0642
Smaller LVEDD	<0.001			
Smaller Indexed LVEDD	<0.001	0.38	(0.15 , 0.86)	0.0456
Smaller LVESD	<0.001			
Smaller Indexed LVESD	<0.001	7.60	(1.51 , 16.11)	0.0095
Changes in LVEDD[a]	0.561			
Changes in LVESD [a]	0.669			
Changes in EF [a]	0.792			
IVSd	0.372			
IVSs	0.568			
LV mass	0.400			
RVP	0.265			

IVSd, Diastolic interventricular septal thickness ; IVSs, Systolic interventricular septal thickness ; PWd, Diastolic posterior wall thickness ; PWs, Systolic posterior wall thickness ; RVP, Right ventricular pressure ;

OR, Odds ratios

[a], Changes in, Difference between immediate postoperative and preoperative echocardiograph

Using receiver-operating characteristics curves, we found that the sensitivity and specificity for predicting normalization of EF early after AVR were 86% and 71% for indexed LVEDD (< 44.4mm/m^2), 68% and 91% for indexed LVESD (<35.3mm/m^2) (Figure 2).

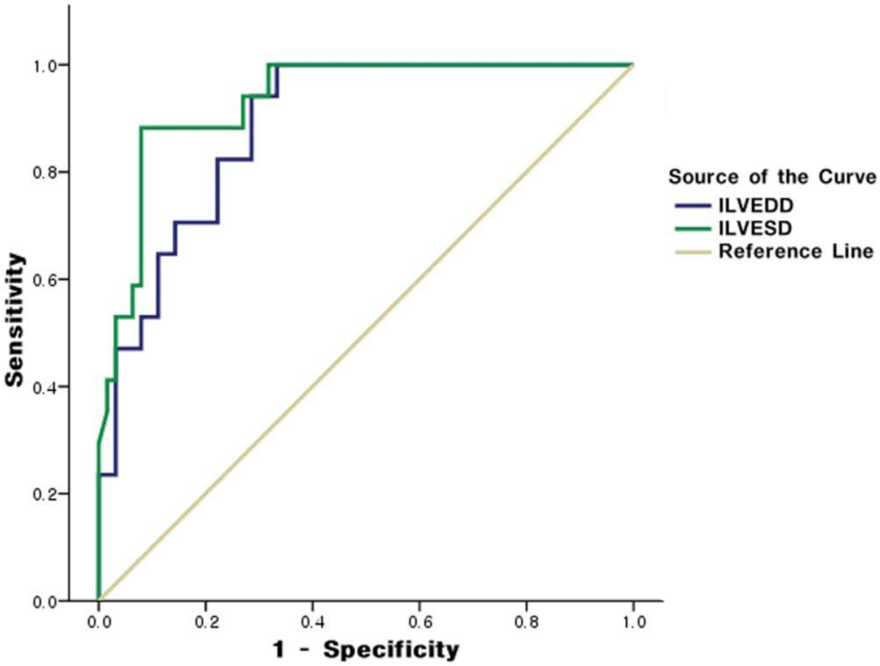

Figure 2. Receiver-operating characteristic curves of Indexed LV dimension. Best cut-off values with normalization of early postoperative EF. < 44.4mm/m^2 for ILVEDD and < 35.3mm/m^2 for ILVESD. Areas under curves were 0.887 and 0.933, respectively

ILVEDD, indexed LVEDD ; ILVESD, indexed LVESD

IV. DISCUSSION

In patients with severe chronic AR, the presence of symptoms is considered a class I indication for AVR. In asymptomatic patients, surgery is recommended when LV dysfunction, defined as end-systolic diameter (ESD), is greater than 50-55 mm and/or EF is less than 50%.[5] These guidelines are based on previous studies reporting that LV dimensions and preoperative systolic function are important predictors of postoperative prognosis. Recent studies have suggested the use of indexed LV dimensions in chronic AR to optimize surgical indications because decisions based on raw data may be inappropriate for patients with extreme body surface area values.[11-12] Sambola et al. showed that indexed ESD (IESD$\geq$25 mm/m^2) predicts unfavorable postoperative outcomes more accurately than ESD (ESD >50 mm) in patients with AR.[11] This effect is more pronounced in patients with low body surface area. Actually, Asian hearts are small compared with the reference values in the guidelines from the American Society of Echocardiography and BSA is also significantly low.[13] Other investigators showed that larger indexed LV dimensions were associated with late mortality, indicating the importance of indexed values.[12] In the present study, we therefore assessed the postoperative course of patients with isolated, severe AR combined with LV systolic dysfunction. We also evaluated several predictors containing indexed values of echocardiographic parameters following AVR.

Mortality and late survival Earlier studies showed that patients with markedly low EF (<35%) or dilated LV constitute a high-risk group even after successful surgery.[8-9, 12] Similarly, Chaliki et al. reported that low EF is associated with excessive operative mortality (OR 4.3) and long-term mortality (OR 2.3) compared with normal EF.[8] Even when excluding operative mortality rates, the risk ratio for expected mortality with low EF was 3.2 compared with 1.4 for normal EF.[8] Klodas et al. showed that extreme LV dilatation was not predictive of mortality and overall survival, and that preoperative low EF was an independent predictor of survival.[9] Brown et al. showed that decreased LVEF and increased LV dimensions were not associated with late mortality, but that larger indexed LV systolic and diastolic dimensions predicted late mortality.[12] A study at the Cleveland Clinic, however, reported no significant difference in operative mortality and long-term survival in patients with LV dysfunction (EF <35%) who underwent surgery after 1985 compared with patients with preserved LV function.[14] The declining operative mortality for such patients is most likely due to multifactorial causes, such as improvements in surgical and anesthetic techniques, early surgery, cardioprotection, prosthetic valve design, postoperative care, and concomitant medical therapy. This result is consistent with the present study, in which operative mortality was 3.7% for patients with LV dysfunction. Regarding overall survival (operative and late deaths combined), there was no significant difference between the 79 patients of our study group and patients with preserved LV function and LV dimension. We were unable to identify predictors for mortality and late survival.

Improvement in LV systolic function after AVR Enlarged LV dimension is usually reduced within the first few weeks after correction of aortic regurgitation, but ejection fraction also decreases at approximately the same time because the effect of preload change is likely to be dominant at this time.[9, 15-17] However, ejection fraction eventually returns to or surpasses preoperative values. This change may be a result of the reduced afterload with gradual improvement in left ventricular function, possibly related to regression of left ventricular hypertrophy after aortic valve replacement, or it may represent an actual improvement in contractile function.[8-9, 15-16, 18] In patients with a significantly dilated ventricle and impaired systolic function, surgery sometimes results in persistent LV dilatation and LV systolic dysfunction.[6-9, 17, 19] Because LV functional recovery after AVR is associated with relief of symptoms and prognosis in patients with chronic AR, it is useful to know preoperative predictors for LV functional recovery after AVR.[1, 9, 12] Several studies have demonstrated that early postoperative status substantially influences long-term outcomes. Thus, patients who have an increase in LVEF within a few months after AVR for AR can expect further improvement in ventricular function.[6, 9, 16] Fewer studies, however, have focused on the effect of preoperative status on early recovery of LV function. Previous investigators reported that preoperative EF was the only significant independent predictor of late recovery of LV function.[9, 12] In contrast, the our present study evaluated the early postoperative course in patients with preexisting LV dysfunction. Mean EF was increased from 49% to 55% at early follow-up, and LVESD and LVEDD were significantly decreased (52.3±8.4 mm vs. 37.8±6.9 mm and 69.6±7.8 mm vs.

51.6±6.4 mm, respectively). Despite correction of severe regurgitation, LV function was not restored in 22% of the patients; this result was associated with large preoperative indexed LV dimensions. Although our findings were not statistically significant (P=0.06), we could not rule out preoperative EF as predictor of early outcomes. Therefore, this issue for the preoperative EF requires further evaluation

Clinical implication In chronic isolated AR, AVR should ideally be performed before severe EF decrease and LV dilatation. Previous studies demonstrated that persistent ventricular dilatation and dysfunction identifies patients at risk of death from congestive heart failure.[17, 19] Recently, operative mortality and overall survival was shown to decline after AVR in a high-risk group. Therefore, we prefer surgical correction over medically conservative care even in high-risk patients. On the basis of oufindings and those of other investigators, early surgical treatment may be important for postoperative clinical outcomes even in the patients with severe LV dilatation and LV dysfunction, considering indexed LV dimensions. In the present study, the cut-off values of ROC curves for indexed LV dimensions were not indicators of surgical correction, but indicate the upper limit for delaying AVR. Patients with indexed LVEDD >44.4 mm/m^2 and indexed LVESD >35.3 mm/m^2 had only a 29% and 9% chance of normalization of LVEF after AVR, respectively. Our findings strongly support the usefulness of Indexed LVESD in the management of patients with chronic AR and showed a high rate of expected adverse course in the subgroup of patients with larger indexed LVESD.

Limitation There are several limitations in this study. First, this study is a retrospective study. In addition, we did not evaluate preoperative predictors for midterm or long-term LV function because mid-term or late follow-up echocardiograms were obtained in only 50 of the 79 patients. However, previous studies demonstrated that early postoperative recovery of LV function was independently associated with long-term outcome and relief of symptoms. Postoperative NYHA functional class changes were not available for all patients; therefore, we were unable to determine the relationship between recovery of LV function and improvement of heart failure symptoms.

Our study group was made up of patients with LV dysfunction. Preoperative LV systolic dysfunction is generally defined as EF < 50% ; however, in the present study, EF was 50-60% in 30 of the 79 patients, but LV dimension was enlarged and global LV hypokinesia was detected by echocardiography. In aortic regurgitation, an abnormally increased preload by large regurgitant volume and altered afterload may result in a overestimated ejection fraction despite underlying myocardial dysfunction (the likelihood of a decrease of 10 to 20%).[15]

V. CONCLUSION

In patients who received a valve replacement for chronic aortic regurgitation, it has been known that decreased LVEF and larger LV dimensions may worsen the survival after AVR. However we reported no significant difference in operative mortality and long-term survival in patients with LV dysfunction compared with patients with preserved LV function.

Because LV functional recovery after AVR is associated with relief of symptoms and prognosis in patients with chronic AR, it is useful to know preoperative predictors for LV functional recovery after AVR. Smaller indexed LV systolic dimension and preoperative preserved EF were associated with early restoration of LV function after AVR. Thus, indexed LV dimension evaluated along with symptoms and LVEF may help predict postoperative clinical course and prognosis for patients with chronic AR.

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ABSTRACT(IN KOREAN)

만성 대동맥판막 폐쇄부전 환자에서 대동맥 판막 치환술 후 좌심실의 조기 기능 회복에 관련된 술전 인자 평가

< 지도교수 유 경 종 >

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조 상 호

만성 대동맥판막 폐쇄부전에서 대동맥판막 치환술 후에 좌심실 용적의 감소 및 좌심실 기능의 회복을 얻을 수 있다. 본 연구에서는 수술 전 심장 기능의 저하가 있었던 만성 대동맥판막 폐쇄부전 환자에서 대동맥판막 치환술 후 심실기능의 회복에 영향을 주는 수술 전 인자에 관하여 연구해 보고자 한다.

1997 년부터 2007 년까지 만성 대동맥판막 폐쇄부전으로 대동맥판막 치환술을 시행 받은 171명의 환자 중에 심초음파 검사 결과 수술 전 좌심실의 수축기능 장애가 있거나 좌심실의 확장이 동반된 79명의 환자를 대상으로 하였다. 수술 전 평균 좌심실 구혈율은 49%였고, 평균 좌심실 수축기말 직경이, 확장기말 직경이 69.6±7.8mm 였다. 수술 사망률은 3.7% 였다. 62명의 환자에서 수술 후 좌심실 기능회복을 확인하였다. 대동맥판막 치환술 후 평균 좌심실 구혈율은 49%에서 55%로 유의하게 증가하였고, 좌심실 수축기말 직경은 52.3±8.3mm 에서 32.8±6.9mm 로 감소하였으며, 확장기말 직경은 69.6±7.8mm 에서 51.6±6.4mm 로 유의하게 감소하였다. 다변량 분석 결과 수술 전 신체지수를 보정한 좌심실의 수축기말 직경이 수술 후 심실 기능의 회복을 예측할 수 인자임을 확인하였다.

좌심실 기능저하를 동반한 만성 대동맥판막 폐쇄부전 환자에서 신체지수를 보정한 좌심실의 직경은 대동맥판막 치환술 후 좌심실 회복을 예측할 수 있는 중요한 인자로 생각된다.

핵심되는 말 : 대동맥판막 치환술, 만성 대동맥판막 폐쇄부전증, 좌심실 기능