

Mass Reduction and Functional Improvement of the Left Ventricle after Aortic Valve Replacement for Degenerative Aortic Stenosis

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Background: Left ventricular (LV) hypertrophy caused by aortic valve stenosis (AS) leads to cardiovascular morbidity and mortality. We sought to determine whether aortic valve replacement (AVR) decreases LV mass and improves LV function. **Materials and Methods:** Retrospective review for 358 consecutive patients, who underwent aortic valve replacement for degenerative AS between January 1995 and December 2008, was performed. There were 230 men and 128 women, and their age at operation was 63.2 ± 10 years (30~85 years). **Results:** There was no in-hospital mortality, and mean follow-up duration after discharge was 48.9 months (2~167 months). Immediate postoperative echocardiography revealed that LV mass index and mean gradient across the aortic valve decreased significantly ($p < 0.001$), and LV mass continued to decrease during the follow-up period ($p < 0.001$). LV ejection fraction (EF) temporarily decreased postoperatively ($p < 0.001$), but LV function recovered immediately and continued to improve with a significant difference between preoperative and postoperative EF ($p < 0.001$). There were 15 late deaths during the follow-up period, and overall survival at 5 and 10 years were 94% and 90%, respectively. On multivariable analysis, age at operation ($p = 0.008$), concomitant coronary bypass surgery ($p < 0.003$), lower preoperative LVEF ($< 40\%$) ($p = 0.0018$), and higher EUROScore (> 7) ($p = 0.045$) were risk factors for late death. **Conclusion:** After AVR for degenerative AS, reduction of left ventricular mass and improvement of left ventricular function continue late after operation.

Key words: 1. Aortic valve replacement
2. Aortic stenosis
3. Left ventricular hypertrophy

INTRODUCTION

Degenerative aortic valve stenosis (AS) is one of the most frequently encountered acquired heart disease [1]. The prognosis of symptomatic AS with severe left ventricular hypertrophy is very poor, and expected survival after the development of symptoms, such as dyspnea, syncope and angina, is less than 2 years [2]. Severe AS in elderly is also associated

with a high mortality, and life expectancy of octogenarians with severe AS is known to be less than 1 year [1]. Aortic valve replacement (AVR) employing cardiopulmonary bypass has been the standard treatment for patients with severe AS. Left ventricular (LV) hypertrophy, which is caused by pressure overload of the LV, is believed to increase the risk of heart failure, cerebrovascular accident and sudden death. Left ventricular mass index (LVMI) is an indicator of LV hyper-

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Table 1. Patient profiles

Clinical variables	Value
Age (years)	
Mean±SD (range)	63.2±10 (30~85)
Sex	
Male, No. (%)	230 (64)
Female, No. (%)	128 (36)
Nationality	
Korean, No. (%)	355 (99.2)
Foreigner, No. (%)	3 (0.8)
NYHA Fc, No. (%)	
I	48 (13)
II	208 (58)
III	91 (25)
IV	11 (3)
Preoperative state, No. (%)	
Inotropic agent	16 (4.5)
Mechanical ventilator apply	2 (0.6)
ECMO support	1 (0.3)
Co-morbidities, No. (%)	
Coronary artery disease	48 (13.4)
Hypertension	133 (37)
Diabetics mellitus	55 (15)
CVA	12 (3.4)
COPD	14 (4)
Smoking History	
Current smoker	96 (27)
Ex-smoker	56 (16)
Euroscore	4.9±2.5 (2~15)
Mean±SD (range)	

SD=Standard deviation; NYHA Fc=New York heart association functional class; ECMO=Extra-corporeal membrane oxygenation; CVA=Cerebrovascular accident (stroke); COPD=Chronic obstructive pulmonary disease.

trophy, and LVMI is known to decrease after the reduction of LV afterload by AVR [3]. However, decrease in LVMI after AVR is slow or stagnant in some patients, and late outcome of AVR in this subset is reportedly worse than that of others with rapid regression of LV hypertrophy [4], which may well be attributed to left ventricular diastolic dysfunction and stenotic nature of ventricular hypertrophy with mal-coordination between the LV and prosthetic aortic valve [5]. In this study, we sought to determine the impact of AVR on LV mass and function, and we conducted risk factor analysis for late mortality after AVR.

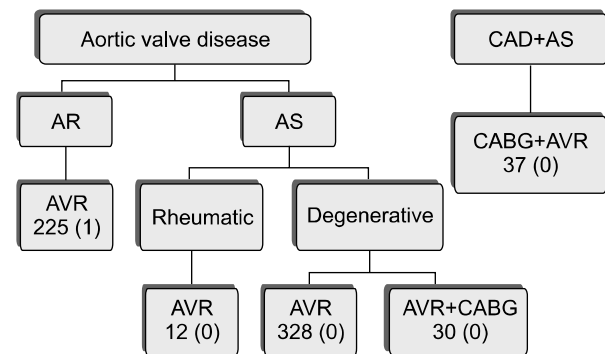


Fig. 1. Aortic valve replacement for various etiologies. AR=Aortic regurgitation; AVR=Aortic valve replacement; AS=Aortic stenosis; CAD=Coronary artery disease; CABG=Coronary artery bypass graft.

MATERIALS AND METHODS

Among the 407 patients who underwent AVR for AS from January 1995 to December 2008, 358 patients were selected for the analysis after excluding 12 with rheumatic valvular heart disease and 37 patients who underwent coronary artery bypass surgery with concomitant AVR for moderate AS which did not correspond to our indications for AVR (Fig. 1). There were 230 men and 128 women, and their age at operation was 63.2±10 years (30~85 years). Among them, 102 patients (102/358, 28.5%) were older than 70 years, and 12 (12/358, 3.5%) were older than 80 years. Preoperative variables, such as New York heart association (NYHA) functional class, smoking history, European system for cardiac operative risk evaluation (Euroscore) [6], and the presence of co-morbidities, such as cerebrovascular disease, coronary artery disease, hypertension, chronic obstructive lung disease, carotid artery obstruction, were reviewed to summarize the clinical characteristics of the cohort and to analyze the risk factors for late death. One-hundred and two (102/358, 28%) were in NYHA class III, 16 were on preoperative inotropic agents, two were on artificial ventilator, and one was on extra-corporeal membrane oxygenation (Table 1). Echocardiography was performed preoperatively and immediate post-operatively to assess the postoperative changes of left ventricular ejection fraction (EF, %), mean gradient across the aortic valve (mmHg), and left ventricular mass indexed by body surface area (g/m²). Follow-up echocardiographic examinations were performed between 6 and 12 months post-

operatively, and annually from then on. Coronary angiography was routinely performed for male patients older than 40 years and female patients older than 45 years. Cardiac computed tomography and carotid doppler examination were also routinely performed for patients older than 60 years to diagnose carotid artery disease and ascending aortic calcification / dilatation.

1) Indications for AVR

Before 2006, AVR was indicated for significant AS, which had been defined as presence of symptoms, aortic valve area of less than 1 cm^2 or mean pressure gradient across the aortic valve of greater than 50 mmHg [7]. From 2006, ACC/AHA guideline [8] has been applied to AVR for AS, that is, presence of symptoms, mean systolic pressure gradient across the aortic valve of greater than 40 mmHg, peak systolic flow velocity across the aortic valve of greater than 4 m/sec, and the association of coronary artery disease which necessitates surgical intervention. For the diagnosis of concealed severe AS in patients with LV dysfunction and low trans-aortic pressure gradient, dobutamine stress echocardiography was conducted.

2) Surgical technique

Under general anesthesia and installation of trans-esophageal echocardiography probe, surgical procedures were performed through median sternotomy and moderately hypothermic cardiopulmonary bypass. Supra-annular prosthetic valve implantation technique has been employed from 2003. In principle, tissue valves were used for the elderly (>65 years) and mechanical valves were used in the younger patients.

3) Statistical analysis

Data were presented as mean with standard deviation or median with ranges. To compare the preoperative and immediate postoperative echocardiographic data, paired t-test was used. To assess the trends of changes in echocardiographic data during the follow-up period, repeated measure ANOVA (analysis of variance) was used. Survival was plotted using Kaplan-Meier method, and risk factors for late death were analyzed by Cox proportional hazards model. Preoperative and operative variables, such as age at operation, sex, presence of

coronary artery disease, NYHA functional class of III or IV, Euroscore of greater than 7, postoperative pressure gradient across the aortic valve of greater than 20 mmHg, preoperative LVEF of lower than 40%, and concomitant coronary bypass surgery, were included for the risk factor analysis of late death. A p-value of less than 0.05 was considered significant, and SPSS (Version 17.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

RESULTS

There was no in-hospital mortality, and mean follow-up duration after discharge was 48.9 months (2~167 months). Follow-up was complete in 97% of the patients, and most of them (83%) have been followed up in our institution. Survival of the patients who were missing from follow-up (2.7%) was ascertained using the database from the 'Statistics Korea'. Immediate postoperative echocardiography revealed that LV mass index decreased significantly ($156 \pm 48.6 \text{ g/m}^2$ to $140 \pm 5.2 \text{ g/m}^2$, $p < 0.001$), and LV mass continued to regress during the follow-up period ($p < 0.001$) (Table 2, Fig. 2). Mean pressure gradient across the aortic valve decreased significantly on immediate postoperative echocardiography ($57.9 \pm 17.6 \text{ mmHg}$ to $13.5 \pm 5.2 \text{ mmHg}$, $p < 0.001$), and remained lower than preoperative value during the follow-up period ($p < 0.001$) (Table 2, Fig. 3). The use of Medtronic-halls valve was associated with significantly greater decrease in mean pressure gradient across the aortic valve compared to the use of ATS (advancing the standard) valve ($p < 0.005$) (Table 3). Preoperative LV ejection fraction (LVEF) was $55 \pm 11\%$, including 33 patients in 30~40% range and 12 patients lower than 30%. Mean LVEF temporarily decreased postoperatively ($58 \pm 13\%$ to $55 \pm 11\%$, $p < 0.001$), but LV function recovered immediately and continued to improve with a significant difference between preoperative and postoperative EF ($p < 0.001$) (Table 2, Fig. 2). There were 15 late deaths during the follow-up period: six died of malignant neoplasm, 3 died of congestive heart failure and 2 died of cerebrovascular accident (Table 4). Overall survival at 5 and 10 years were 94% and 90%, respectively. Among the 3 patients who died of congestive heart failure, 2 had preoperative LVEF of lower than 40%. On univariable analysis, age at op-

Table 2. Echocardiographic findings

LV mass (g/m ²)								
	Pre (n=319)	Post (n=304)	p-value	0.5~1.5 yr (n=241)	1.5~3 yr (n=149)	3 yr< (n=69)	p-value*	
Mean	156	140	<0.001	112	103	104		
SD	49	42		33	26	26		
Median	150	137		108	99	100	<0.001	
Min	59	60		47	55	65		
Max	386	312		305	186	177		
Mean pressure gradient of AoV (%)								
	Pre (n=348)	Post (n=350)	p-value	0.5~1.5 yr (n=258)	1.5~3 yr (n=149)	3~5 yr (n=77)	5 yr~ (n=57)	p-value*
Mean	57.93	13.49	<0.001	12.92	13.22	14.85	16.88	
SD	17.58	5.19		5.49	6.02	5.95	7.40	
Median	55	13		12	12	14	15	<0.001
Min	17	4		3	3	3	7	
Max	122	48		48	47	29	44	
≥20		31		24	9	14	14	
LVEF (%)								
	Pre (n=323)	Post (n=302)	p-value	0.5~1.5 yr (n=241)	1.5~3 yr (n=137)	3~5 yr (n=73)	5 yr~ (n=56)	p-value*
Mean	58	54.90	<0.001	62.53	63.59	62.91	64.23	
SD	13	10.85		8.15	7.38	6.46	5.62	
Median	61	56		63	65	63	64	<0.001
Min	15	24		28	43	50	55	
Max	86	82		81	80	78	75	

LV=Left ventricular; SD=Standard deviation; AoV=Aortic valve; LVEF=Left ventricular ejection fraction; *Comparison of early and late follow-up.

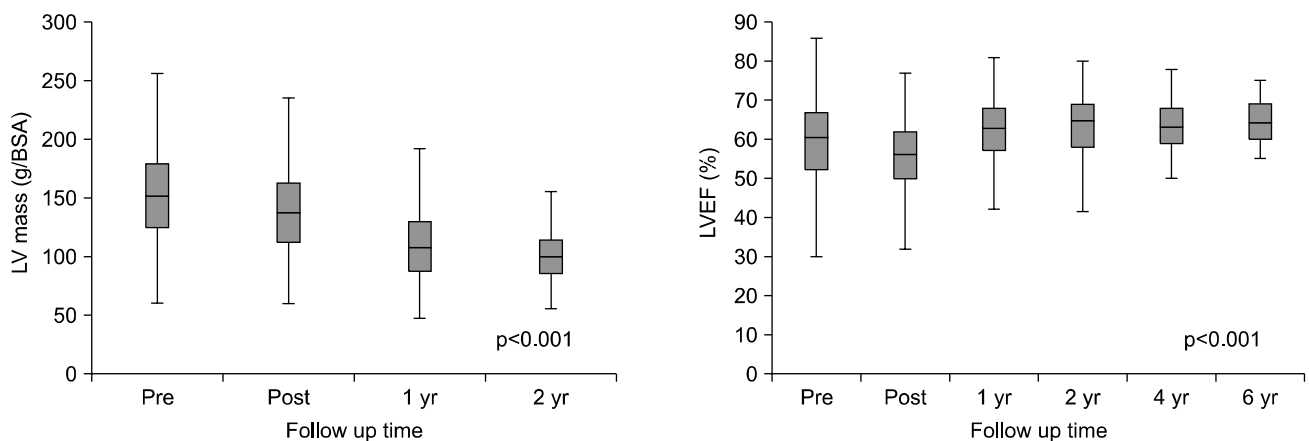


Fig. 2. Postoperative changes of left ventricular mass index and ejection fraction. LV=The left ventricle; LVEF=Left ventricular ejection fraction.

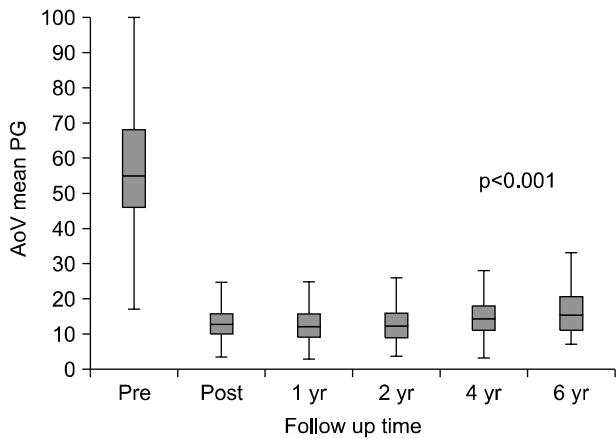


Fig. 3. Postoperative changes of pressure gradient across the aortic valve. AoV=The aortic valve; PG=Pressure gradient.

Table 3. Mean trans-aortic PG according to the types of prosthetic aortic valve

Valve	No.	Mean PG of aortic valve (mmHg)±SD	
		Preoperative	Immediate postoperative
Mechanical (45%)	163		
ATS	37	61.6±23	16.2±9
Med-Hall	32	59.3±17	11.1±4
On-X	35	64.2±17	11.9±4
St. Jude Regent	54	53.7±15	12.3±5
Others	5		
Tissue (55%)	195		
CE Perimount	61	61.6±18	14.7±4
CE Magna	110	55.8±16	13.8±5
Others	21		

PG=Pressure gradient; SD=Standard deviation; ATS=Advancing the standard; CE=Carpentier-Edwards.

eration ($p=0.005$), concomitant coronary bypass surgery ($p<0.001$) and preoperative LVEF of lower than 40% ($p=0.0037$) were risk factors for late death. On multivariable analysis, age at operation ($p=0.008$), concomitant coronary bypass surgery ($p<0.003$), preoperative LVEF of lower than 40% ($p=0.0018$), and EUROScore ($p=0.045$) were risk factors for late death (Table 5).

Table 4. Causes of late mortality

Variable	No. of patients (%)
Late mortality	15 (4)
Causes of mortality	
Malignancy	6 (1.7)
Congestive heart failure	3 (0.8)
CVA	2 (0.6)
Liver cirrhosis	1 (0.3)
Biliary sepsis	1 (0.3)
Sudden death	1 (0.3)
Unknown	1 (0.3)

CVA=Cerebrovascular accident (stroke).

Table 5. Risk factors for late death

Clinical variable	Univariate analysis	Multivariate analysis
	p-value	p-value
Sex	0.277	
Age	0.005	0.008
Coronary artery disease	0.081	
Previous MI	0.001	0.003
NYHA Fc III-IV	0.333	
Euroscore	0.066	0.045
Preoperative LVEF (%)	0.037	0.018
Postoperative AoV mean PG (≥ 20)	0.240	
Concomitant CABG	<0.001	0.006

MI=Myocardial infarction; NYHA Fc=New York heart association functional class; LVEF=Left ventricular ejection fraction; AoV=Aortic valve; PG=Pressure gradient; CABG=Coronary artery bypass grafting surgery.

DISCUSSION

Ventricular hypertrophy is an adaptation process of the left ventricle (LV) to cope with chronic pressure overload caused by aortic stenosis. In the earlier phase, ventricular hypertrophy is beneficial for the generation of adequate stroke volume and cardiac output across the stenotic aortic valve, but prolonged exposure to severe pressure overload leads to afterload mismatch with ventricular systolic dysfunction and decreased pressure gradient across the aortic valve. In this setting, aortic valve replacement (AVR) is known to alleviate heart failure symptoms and improve left ventricular function [9,10]. Adequate dimension of the left ventricular outflow

tract (LVOT) is the key to successful outcome because inappropriate size of the prosthetic AV is the main cause of residual pressure gradient across the AV [11]. However, ventricular hypertrophy, which is attributed to chronic pressure overload to the LV, is believed to be more important prognostic factor than the pressure gradient across the prosthetic AV [12]. In a study pertaining to systemic hypertension, ventricular hypertrophy was associated with decreased survival by myocardial ischemia, systolic and diastolic dysfunction, and ventricular arrhythmia which may lead to sudden death [13,14]. To the contrary, AVR for aortic stenosis is reportedly associated with left ventricular mass reduction, stabilization of the ventricular electrical instability, and improvements in myocardial ischemia, and, hence, improved functional capacity and long-term outcome [11]. In this study, reduction of the ventricular mass was observed immediately postoperatively, and LV mass continued to regress as time passed. Delay in the improvements in LV ejection fraction is believed to be associated with myocardial fibrosis [15].

Mortality after AVR in octogenarians has reportedly decreased from 14% [16] to 2.4~5% [17,18], which is consistent with the results from this study. In our series, there was no early mortality regardless of the age at operation or the presence of associated cardiac diseases, and one of the major causes of late deaths was malignancy. Three patients died of congestive heart failure, two of whom showed decreased LV ejection fraction (<40%) preoperatively. risk factors for late death turned out to be age at operation, concomitant coronary artery bypass surgery, and preoperative LV dysfunction (LV ejection fraction <40%). In other reports, postoperative changes in NYHA functional class [19] and pressure gradient across the AV [20] were identified as prognostic factors for late survival.

One of the peri-operative factors which excellent early and late outcome of this series could be attributed to is our vigorous attempts to ascertain any calcification in the thoracic aorta. To this end, we routinely conducted preoperative cardiac computed tomography, intra-operative transesophageal echocardiographic monitoring, and, more recently, intra-operative epiaortic echocardiography prior to the surgical intervention of the aorta. Relatively younger age at operation compared to other series, AVR by cardiac surgeons who ex-

clusively perform valve surgery, and higher valve size-body weight ratio with lower postoperative residual trans-aortic pressure gradient could well be contributing factors for better outcome too. To implant bigger-sized prosthetic valves, we have employed supra-annular valve implantation technique and aortic annulus enlargement procedures. Thanks to these aggressive maneuvers, only 24 patients (6.7%) showed residual mean trans-aortic gradient greater than 20 mmHg on postoperative one-year echocardiography (Table 2). Retrospective study design, and, as a result, significant missing data in the earlier cohort, are limitations of this study.

CONCLUSION

After aortic valve replacement, left ventricular mass index significantly decreased immediately postoperatively and continued to decrease, while left ventricular function deteriorated immediately postoperatively but gradually improved during the follow-up period. Lower preoperative left ventricular ejection fraction was identified as a risk factor for late mortality.

REFERENCES

1. Varadarajan P, Kapoor N, Bansal RC, Pai RG. *Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: Results from a cohort of 277 patients aged > or =80 years.* Eur J Cardiothorac Surg 2006;30:722-7.
2. Horstkotte D, Loogen F. *The natural history of aortic valve stenosis.* Eur Heart J 1988;9 Suppl E:57-64.
3. Turina J, Turina M, Rothlin M, Krayenbuehl HP. *Improved late survival in patients with chronic aortic regurgitation by earlier operation.* Circulation 1984;70:1147-52.
4. Lund O, Kristensen LH, Baandrup U, et al. *Myocardial structure as a determinant of pre- and postoperative ventricular function and long-term prognosis after valve replacement for aortic stenosis.* Eur Heart J 1998;19:1099-108.
5. Yoganathan AP, Woo YR, Williams FP, Stevenson DM, Franch RH, Harrison EC. *In vitro fluid dynamic characteristics of Ionescu-Shiley and Carpentier-Edwards tissue bioprostheses.* Artif Organs 1983;7:459-69.
6. Roques F, Nashef SA, Michel P, et al. *Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients.* Eur J Cardiothorac Surg 1999;15:816-22.
7. Bonow RO, Carabello B, de Leon AC, et al. *ACC/AHA*

- guidelines for the management of patients with valvular heart disease. Executive Summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on management of patients with valvular heart disease). *J Heart Valve Dis* 1998; 7:672-707.
8. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2006;48:e1-148.
 9. Connolly HM, Oh JK, Orszulak TA, et al. Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. Prognostic indicators. *Circulation* 1997;95:2395-400.
 10. Pantely G, Morton M, Rahimtoola SH. Effects of successful, uncomplicated valve replacement on ventricular hypertrophy, volume, and performance in aortic stenosis and in aortic incompetence. *J Thorac Cardiovasc Surg* 1978;75:383-91.
 11. Gonzalez-Juanatey JR, Garcia-Acuna JM, Vega Fernandez M, et al. Influence of the size of aortic valve prostheses on hemodynamics and change in left ventricular mass: implications for the surgical management of aortic stenosis. *J Thorac Cardiovasc Surg* 1996;112:273-80.
 12. Ota T, Iwahashi K, Matsuda H, Tsukube T, Ataka K, Okada M. Reduction of left ventricular hypertrophy with St. Jude Medical 19 mm valve prosthesis. *Angiology* 1995;46:981-7.
 13. Sullivan JM, Vander Zwaag RV, el-Zeky F, Ramanathan KB, Mirvis DM. Left ventricular hypertrophy: effect on survival. *J Am Coll Cardiol* 1993;22:508-13.
 14. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994;90:1786-93.
 15. Hwang MH, Hammermeister KE, Oprian C, et al. Preoperative identification of patients likely to have left ventricular dysfunction after aortic valve replacement. Participants in the Veterans Administration Cooperative Study on Valvular Heart Disease. *Circulation* 1989;80:165-76.
 16. Olsson M, Granström L, Lindblom D, Rosenqvist M, Rydén L. Aortic valve replacement in octogenarians with aortic stenosis: a case-control study. *J Am Coll Cardiol* 1992;20: 1512-6.
 17. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg* 2009;137:82-90.
 18. Malaisrie SC, McCarthy PM, McGee EC, et al. Contemporary perioperative results of isolated aortic valve replacement for aortic stenosis. *Ann Thorac Surg* 2010;89:751-6.
 19. Connolly HM, Oh JK, Schaff HV, et al. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. *Circulation* 2000;101:1940-6.
 20. Carabello BA, Green LH, Grossman W, Cohn LH, Koster JK, Collins JJ Jr. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. *Circulation* 1980;62:42-8.