A CLINICAL STUDY OF ISOLATED AORTIC VALVE REPLACEMENT: A UNIVARIATE ANALYSIS OF RISK FACTORS

REPUBLIC OF KOREA

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ABSTRACT

Between 1979 and 1990, 190 patients underwent isolated aortic valve replacement at Seoul National University Hospital in Korea. There were 11 (5.8%) in-hospital deaths. Univariate analysis identified advanced age ($p = 0.026$), preoperative serum GOT or GPT greater than 40 IU/l ($p < 0.001$, $p = 0.003$), NYHA Class III or IV ($p = 0.029$), preoperative mean pulmonary arterial pressure greater than 19 mmHg ($p = 0.019$), reoperation for aortic valve replacement ($p = 0.035$), second or third open heart surgery ($p < 0.001$), and use of mechanical valve ($p = 0.008$) as variables associated with increased in-hospital risk. Follow-up documented survival rates of 98.1% and 96.4% and event-free survival rates of 95.7% and 81.6% at 3 and 7 postoperative years, respectively. NYHA Class III or IV ($p = 0.009$), preoperative serum total bilirubin level greater than 1.2 mg/dl ($p = 0.009$), reoperation for aortic valve replacement ($p = 0.03$), second or third open heart surgery ($p = 0.002$), and use of mechanical valve were associated with decreased late survival and event-free survival.

INTRODUCTION

The results of aortic valve replacement have improved dramatically. Operative mortality was 10% to 30% in the early 1970s; but mortality in the 1980s was less than 5%.[1,2] The improved results were due not only to improved surgical techniques, but to routine perioperative hemodynamic monitoring, improved anesthetic techniques and myocardial protection, and early referral with development of noninvasive investigations.[3] To examine the effect of multiple preoperative and intraoperative variables on in-hospital and late results, we reviewed 190 patients who underwent primary aortic valve replacement at Seoul National University Hospital in Korea from 1979 through 1990.

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MATERIALS AND METHODS

The medical records of 190 patients older than 15 years, who underwent primary isolated aortic valve replacement from 1979 through 1990, were reviewed. We excluded simultaneous cardiac and noncardiac operations other than aortic valve replacements (simultaneous mitral valve annuloplasty, mitral valve replacement, Bentall operation or modified Bentall operation, and CABG or operations for associated congenital heart disease were excluded). Preoperative, operative, and postoperative in-hospital data were obtained from hospital records. The variables examined are listed in Table 1.

TABLE 1. VARIABLES TESTED FOR ASSOCIATION WITH EARLY AND LATE RISK

- Preoperative clinical variables
  - Age
  - Sex
  - Preoperative NYHA function class
  - Duration of Sx.
  - Atrial fibrillation
  - BUN
  - Creatinin
  - GOT
  - GPT
  - Total bilirubin
- Valve lesion
  - Stenosis
  - Insufficiency
  - Mixed
  - Associated with SBE
  - Prosthetic valve failure
- Preoperative echocardiogram variables
  - Ejection fraction (EF)
  - Left ventricular enddiastolic dimension
- Preoperative catheterization variables
  - Left ventricular enddiastolic dimension
- Preoperative catheterization variables
  - Left ventricular enddiastolic pressure
  - Pulmonary artery pressure (mean)
  - Pulmonary artery pressure (systolic)
  - Pulmonary wedge pressure
- Operation-related variables
  - Frequency of operation
  - Aortic valve prosthesis
    - mechanical vs. bioprosthesis
  - Cardiopulmonary bypass time
  - Aorta cross-clamping time

There were 140 male and 50 female patients ranging in age from 15 to 67 years (mean 40.2 ± 2.1 years). Aortic valve lesions were classified as stenosis, insufficiency, mixed, and associated with SBE, and prosthetic valve failure was based on preoperative cardiac angiogram and catheterization, echocardiogram, preoperative clinical findings, and intraoperative pathology. (Catheterization data for 40 patients were not available.)

Thrombosed prosthetic valve, pannus formation, mechanical dysfunction, paravalvular leakage, calcification, infected prosthetic valve, and tearing of valve leaflet were classified as prosthetic valve dysfunction. The lesions associated with SBE were defined based on positive blood culture, identification of organisms at valves, and pathology. All patients underwent cardiopulmonary bypass, and moderate hemodilution and systemic hypothermia were maintained during bypass. Intermittent, multiple, and cold cardioplegia were employed for myocardial protection.

TABLE 2. PROSTHETIC VALVE USED

Valve	Cases	Average Size of Valve
Ionescu-Shiley	73	23.3 mm
Hancock	4	25.0 mm
Björk-Shiley	13	24.7 mm
Duromedics	4	24.5 mm
St. Jude	59	23.8 mm
CarboMedics	37	24.0 mm
Total	190	23.7 mm

Prosthesis selection was based primarily on surgeon's preference. Before 1984, only bioprosthetic valves were used. For the entire group, the following aortic valve prostheses were used: Ionescu-Shiley, 73 valves; Hancock, 4; Björk-Shiley, 13; Duromedics, 4; St. Jude, 59; and CarboMedics, 37 (Table 2). The frequency of open heart surgery and previous open heart surgery is shown in Table 3. The prosthetic valves used in previous aortic valve replacements were Ionescu-Shiley, 8 valves; Hancock, 4; St. Jude, 5; and Björk-Shiley, 2.

Patients with mechanical prostheses routinely received warfarin, and patients with bioprostheses did not receive warfarin unless there were other indications for anticoagulation. Follow-up information was obtained on survivors during office visits or by telephone interviews with the patient or a relative of the patient. Fourteen patients (7.7%) were lost to follow-up. Cumulative patient follow-up was 648.5 patient-years, and mean duration of follow-up was 47 ± 31.7 months.

STATISTICAL ANALYSIS

The data are presented univariantly by logistic regression for early events and univariantly by the Cox proportional hazards survival analysis for late events. Patient survival is expressed by the life-table method.

TABLE 3. PREVIOUS OHS

Operation Name	Frequency	Cases
AVR	1	10
DVR	1	4
VSD patch closure	1	2
AVR + VSD patch closure	1	1
AVR + MAP	1	1
MVR + TAP	1	1
Open aortic valvotomy	1	1
VSD patch closure, AVR	2	1
DVR, AVR	2	1
AVR, MVR	2	1
Total	13	23

DVR: double valve replacement; MAP: mitral annuloplasty; TAP: tricuspid annuloplasty

RESULTS

EARLY RESULTS

Among the 190 patients in the series, there were 11 (5.8%) in-hospital deaths. Modes of in-hospital death were low cardiac output, 5 patients; sepsis, 3 patients; thromboembolism, 1 patient; arrhythmia, 1 patient; and sudden in-hospital death, 1 patient.

There were 23 early complications in 22 patients (12.7%). The complications were reoperation for postoperative bleeding, 7 patients; IABP support for low output syndrome, 3 patients; thromboembolism, 1 patient; post-pericardiostomy syndrome, 1 patient; and reoperation for paravalvular leakage, 1 patient.

The variables listed in Table 1 were examined with univariate analyses for their association with in-hospital mortality or morbidity (Table 4). Univariate testing indicated these variables were associated with increased risk: advanced age (p = 0.026, patients aged 40 years or older

TABLE 4. PREOPERATIVE AND OPERATIVE VARIABLES AND IN-HOSPITAL MORTALITY AND MORBIDITY

Variable	% Mortality or Morbidity	Variable	% Mortality or Morbidity
Age (years)		Total bilirubin (mg/100 ml)	
<40	11.5%	<1.2	12.9%
>40	22.3%	>1.2	21.4%
	p = 0.026		p = 0.220
Sex		LVEDD (mm)	
Male	16.4%	<70	20.5%
Female	20.0%	>70	23.4%
	p = 0.401		p = 0.237
Preop. FC (NYHA)		EF	
I, II	8.9%	>0.5	17.0%
III, IV	25.7%	<0.5	25%
	p = 0.029		p = 0.217
Sx. duration (months)		LVEDP (mmHg)	
<36	19.4%	<20	15.3%
>36	13.3%	>20	21.2%
	p = 0.242		p = 0.597
Preop. AF		PAP (systolic, mmHg)	
(+)	37.5%	<31	9.5%
(-)	16.5%	>31	21.3%
	p = 0.120		p = 0.067
Valve lesion		PAP (mean mmHg)	
stenosis	15.0%	<19	8.8%
insufficiency	14.0%	>19	25.5%
mixed lesion	9.1%		p = 0.019
associated with SBE	21.7%	PWP (mean, mmHg)	
prosthetic valve failure	47.4%	<9	11.5%
(redo AVR)		>9	16.4%
	p = 0.035		p = 0.502
	(prosthetic valve failure)	Valve prosthesis	
BUN (mg/100 ml)		bioprosthesis	6.3%
<26	16.7%	mechanical valve	25.2%
>26	17.4%		p = 0.008
	p = 0.949	OP frequency	
Cr (mg/100 ml)		1	12.6%
<1.4	16.5%	>1	52.2%
>1.4	17.4%		p < 0.001
	p = 0.752	CPB time (min)	
GOT (U/L)		<100	8.0%
<40	13.3%	>100	26.0%
>40	60.0%		p = 0.016
	p < 0.001	ACC time (min)	
GPT (U/L)		<80	14.0%
<40	14.4%	>80	23.0%
>40	46.7%		p = 0.283
	p = 0.003		

LVEDD: left ventricular enddiastolic dimension; LVEDP: left ventricular enddiastolic pressure; PAP: pulmonary arterial pressure; PWP: pulmonary wedge pressure; CPB: cardiopulmonary bypass; ACC: aorta cross-clamping

TABLE 5. LINEARIZED ANNUAL INCIDENCE OF VALVE-RELATED COMPLICATIONS

	All Complications	Thromboembolism	Prosthetic Valve Endocarditis	Reoperation	Bleeding
All cases	5.24%/pt-yr	1.08%/pt-yr	0.62%/pt-yr	2.16%/pt-yr	0.62%/pt-yr
Ionescu-Shiley	4.34%/pt-yr	0.87%/pt-yr	0.87%/pt-yr	2.02%/pt-yr	0
Hancock	10.59%/pt-yr	0	0	10.49%/pt-yr	0
Björk-Shiley	2.14%/pt-yr	0	0	0	0
Duromedics	0	0	0	0	0
St. Jude	5.90%/pt-yr	0.66%/pt-yr	0	2.62%/pt-yr	1.31%/pt-yr
CarboMedics	9.29%/pt-yr	4.64%/pt-yr	1.55%/pt-yr	0	3.10%/pt-yr

were compared with younger patients); reoperation for valve replacement (p = 0.035); mechanical valve implantation (p = 0.008); 2 or more open heart surgeries (p < 0.001); preoperative NYHA Class III or IV (p = 0.029); preoperative serum GOT or GPT level of greater than 40 IU/l (p < 0.001, p = 0.003); mean pulmonary arterial pressure of greater than 19 mmHg (p=0.019); and cardiopulmonary bypass time of greater than 100 minutes (p = 0.016).

TABLE 6. PREOPERATIVE AND OPERATIVE VARIABLES AND LATE MORTALITY AND MORBIDITY

Risk Factor	p Value	95% Confidence Bounds	
Age > 40 years	0.719		
Sex	0.869		
Valve lesion			
Stenosis			
Insufficiency	0.825		
Mixed	0.816		
Associated with SBE	0.237		
Prosthetic valve failure (redo AVR)	0.032	1.125	7.6
Duration of Sx. > 36 months	0.168		
Preoperative FC III, IV (NYHA)	0.009	1.376	8.917
AF	0.262		
BUN > 26 mg/100 ml	0.754		
Creatinin > 1.4 mg/100 ml	0.754		
GOT > 40 U/L	0.870		
GPT > 40 U/L	0.470		
Bilirubin (total) > 1.2 mg/100 ml	0.010	1.300	7.142
LVEDD > 70 mm	0.116		
EF < 0.5	0.231		
LVEDP > 20 mmHg	0.849		
PAP (systolic) > 31 mmHg	0.364		
PAP (mean) > 19 mmHg	0.215		
PWP (mean) > 13 mmHg	0.778		
Mechanical valve	< 0.001		
ACC time > 80 min	0.203		
CPB time > 100 min	0.148		

LVEDD: left ventricular enddiastolic dimension; LVEDP: left ventricular enddiastolic pressure; PAP: pulmonary arterial pressure PWP: pulmonary wedge pressure; ACC: aorta cross-clamping; CPB: cardiopulmonary bypass

LATE RESULTS

Among 179 operative survivors, 14 patients were lost to follow-up. There were 4 late deaths (2.4%). The modes of late deaths were thromboembolism in the brain, 2 patients; cerebral hemorrhage, 1 patient; and heart failure, 1 patient. There were 33 late complications in 30 patients (18.6%). The complications were reoperation for aortic valve replacement, 14 patients; thromboembolism, 6 patients; endocarditis, 4 patients; NYHA Class III or IV, 4 patients (including patients who did not undergo reoperation for aortic valve replacement during the period under review); arrhythmia, 3 patients; and anticoagulant-related hemorrhage, 2 patients. Linearized occurrence rates of prosthetic valve-related complications are summarized in Table 5. Two reoperations in patients who underwent previous aortic valve replacements with St. Jude valves were due to paravalvular leakage.

The variables listed in Table 1 and early complications were examined by univariate analyses for their association with late mortality and late morbidity (Table 6). Univariate testing indicated that these variables were associated with increased risk: reoperation for valve replacement (p = 0.032); mechanical valve implantation (p < 0.001); 2 or more open heart surgeries (p=0.002); preoperative NYHA Class III or IV (p = 0.009); and preoperative serum total bilirubin level of greater than 1.2 mg/dl (p = 0.009).

SURVIVAL

The actuarial survival rate of all operative survivors was 98.1% at 3 years and 96.4% at 7 years. The actuarial probability of freedom from all prosthetic valve-related complications was 95.7% at 3 years and 81.6% at 7 years (Figure 1). Freedom from valve-related complication was 98.5% at 3 years and 93.3% at 7 years for the bioprosthetic valve, 88.4% at 3 years for the mechanical valve, and 49.5% at 3 years for reoperation of aortic valve replacement (Figure 2).

DISCUSSION

Aortic valve replacement was well-established in the early 1970s. Through the last decade, the indications for aortic valve replacement have continued to expand.

With prolonged life expectancy, more elderly patients are undergoing surgical treatment, and the results are optimal. In our series, there was only 1 operative death (operative mortality, 6.7%) among 15 patients older than 60 years. But age has been reported as the most profound determinant of in-hospital mortality and morbidity. The in-hospital mortality of patients older than 70 years who underwent aortic valve replacement was reported to be 2 to 8 times greater than patients in their 40s.[4-6,8-9] Preoperative NYHA Class is another important risk factor associated with in-hospital mortality and morbidity. The in-hospital mortality of NYHA Class I or II was reported from 0% to 4.2%; whereas that of NYHA Class III or IV was reported to be from 2.5% to 6.8% and from 7% to 14.5%.[1-4,6-9,11]

Patients with aortic regurgitation were at a higher risk for lesions of the aortic valve than those with aortic stenosis, an influence not apparent in our study. It was reported that endocarditis itself is not a determinant of in-hospital risk, but endocarditis in prosthetic valves has been reported as a strong factor, increasing in-hospital risk.[7,9,12]

Increased in-hospital risk for reoperation of aortic valve replacement was apparent in this study. Wideman[11] reported that the in-hospital mortality of patients who underwent reoperation for aortic valve replacement was 3.9%; whereas, the in-hospital mortality of previous operations was 2.9%. In this study, reoperation for aortic valve replacement was a strong determinant of in-hospital risk and late risk. With aortic valve lesion, elevation of pulmonary arterial pressure is due to elevation of left ventricular enddiastolic pressure; but the effect of elevated pulmonary arterial pressure or left ventricular enddiastolic pressure on a patient's prognosis is controversial.[3,4,10] In our study, elevation of mean pulmonary arterial pressure was one of the determinants of in-hospital risk, but elevation of pulmonary wedge pressure or elevation of left ventricular end-diastolic pressure was not associated with in-hospital risk. Preoperative atrial fibrillation, elevation of serum BUN, and elevation of serum creatinin were reported as determinants of in-hospital risk.[3-6] Although increased in-hospital risk for preoperative atrial fibrillation was apparent in this study, this trend did not reach statistical significance; and elevated BUN and creatinin were not associated with in-hospital risk.

Elevation of GOT and GPT were profound determinants of in-hospital risk in this study. However, considering univariant statistical analysis and the fact that mean pulmonary arterial pressure of patients whose BUN and creatinin were elevated was 34 mmHg and 36 mmHg, elevated GOT and GPT due to congestive heart failure were associated with in-hospital risk.

With the mechanical valve, use of cardioplegic solution, previous open heart surgery, and prolonged aortic cross-clamping time have also been reported as in-hospital risk factors.[4,5] In our study, cardioplegic solution was used in all patients, and prolonged aortic cross-clamping time put the patient at higher risk, but this trend did not reach statistical significance. We found prolonged cardiopulmonary bypass time was associated with in-hospital risk. This is due to the support of the cardiopulmonary bypass machine for management of low output during cardiopulmonary bypass weaning.

Age, another profound determinant of in-hospital risk, was also reported as a significant determinant of late survival. Lytle[4] reported a 10-year late survival rate of 78.5% for patients in their 40s and 35.2% in those older than 70 years. In our study, age was not associated with late risk. NYHA Class was also a profound determinant of late survival.

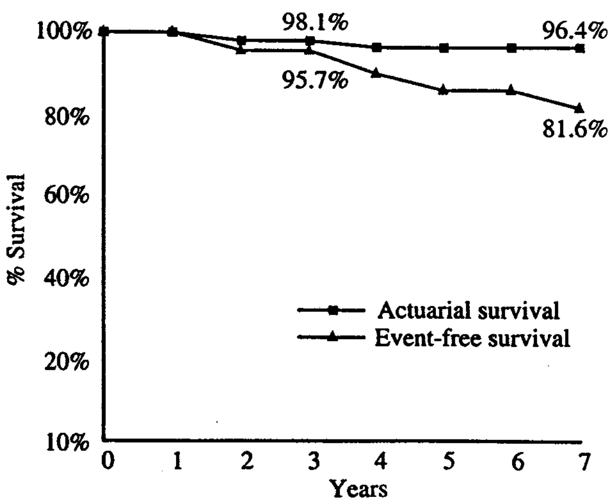

Figure 1. Actuarial survival and event-free survival, in-hospital survivors of isolated aortic valve replacement. Actuarial survival rates were 98.1% and 96.4%, and postoperative event-free survival rates were 95.7% and 81.6% at 3 and 7 years, respectively.

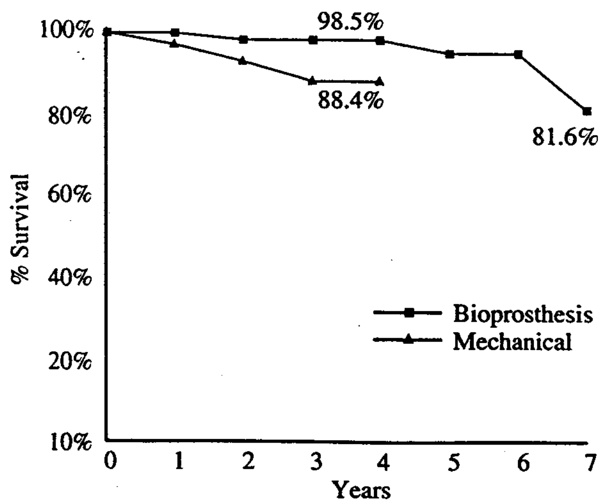

Figure 2. Late survival according to decade of life. Late survival rates decrease significantly each decade of life ($p<0.001$).

With lesions of the aortic valve, in-hospital mortality and late survival rate of patients with aortic regurgitation were reported higher than in patients with aortic stenosis. Patients with aortic valvular heart disease have done well until symptoms appeared. However, during this period, myocardial damage occurs progressively and reaches a dangerous status. This degenerative change of myocardium is more severe in aortic regurgitation than in aortic stenosis. The effect of prosthetic valves on late survival is not certain. Hammermeister[13] found no difference in late survival rate according to the kind of valve. However, Lytle[4] reported the survival rates of patients with bioprostheses at 5 and 10 years were 90% and 66%, and for patients with mechanical valves, 5- and 10-year survival rates were 81% and 61%. He also found that not only late survival, but also the rate of occurrence of late events in patients with mechanical valves was higher than in those with bioprosthetic valves. Borkon[14] reported rates of reoperation and endocarditis were lower for patients with mechanical valves, but the rate of bleeding due to anticoagulation was much higher than in those with bioprosthetic valves; therefore, the rate of late cardiac events for patients with mechanical valves was higher than in those with bioprosthetic valves. In our study, among 4 late deaths, 3 patients underwent valve replacement with mechanical valves.

Performing valve replacement before the occurrence of irreversible change of the myocardium is the keystone for a good outcome. Therefore, ventricular function should be periodically estimated by noninvasive methods such as echocardiogram and exercise tolerance tests for outpatients with aortic valve disease.[3,15] Thereafter, early referral should be required.

CONCLUSION

Further improvements may be possible through the development of noninvasive methods for the evaluation of ventricular function, early referral, improvements in myocardial protection and anesthetic techniques, and more critical indications for operation.

REFERENCES

1. Kay EB, Zimmerman HA, Mendelsohn D Jr. Aortic valvular surgery with artificial valves: an analysis of the first 100 patients. Circulation 1963;27:767-71.
2. Kirklin JW, Barratt-Boyes BG. Aortic valve disease. Cardiac Surgery. New York: John Wiley Sons, 1986.
3. Christakis GT, Weisel RD, Fremes SE, et al. Can the results of contemporary aortic valve replacement be improved? J Thorac Surg 1986;92:37-46.
4. Lytle BW, Cosgrove DM, Taylor PC, et al. Primary isolated aortic valve replacement. J Thorac Cardiovasc Surg 1989;97:675-94.
5. Mitchell RS, Miller DC, Stinson EB, et al. Significant patient-related determinants of prosthetic valve performance. J Thorac Cardiovasc Surg 1986;91:807-17.
6. Scott WC, Miller DC, Haverich A, et al. Determinants of operative mortality for patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 1985;89:400-13.
7. Daenen W, Noyez L, Lesaffre E, Goffin Y, Stalpaert G. The Ionescu-Shiley pericardial valve: results in 473 patients. Ann Thorac Surg 1988;46:536-41.
8. Di Lello F, Flemma RJ, Anderson AJ, Mullen DC, Kleinman LH, Werner PH. Improved early results after aortic valve replacement: analysis by surgical time frame. Ann Thorac Surg 1989;47:51-6.
9. Scott WC, Miller DC, Haverich A, et al. Determinants of operative mortality for patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 1985;89:400-13.
10. Johnson LW, Hapanowicz MB, Buonanno C, Bowser MA, Marvasti MA, Parker Jr FB. Pulmonary hypertension in isolated aortic stenosis. J Thorac Cardiovasc Surg 1988;95:603-7.
11. Louagie Y, Brrohet C, Robert A, et al. Factors influencing postoperative survival in aortic regurgitation. J Thorac Cardiovasc Surg 1984;88:225-33.
12. Wideman FE, Blackstone EH, Kirklin JW, Karp RB, Kouchoukos NT, Pacitico AD. Hospital mortality of rereplacement of the aortic valve: incremental risk factors. J Thorac Cardiovasc Surg 1981;82:692-8.
13. Hammermeister KE, Henderson WG, Burchfiel CM, et al. Comparison of outcome after valve replacement with a bioprosthesis versus a mechanical prosthesis: initial 5 year results of a randomized trial. J Am Coll Cardiol 1987;10:719.
14. Borkon AM, Soule LM, Baughhman KL, et al. Comparative analysis of mechanical and bioprosthetic valves after aortic valve replacement. J Thorac Cardiovasc Surg 1987;94:20-33.
15. Bonow RO, Borer JS, Rosing DR, et al. Preoperative exercise capacity in symptomatic patients with aortic regurgitation as a predictor of postoperative left ventricular function and long-term prognosis. Circulation 1980;62:1280-90.