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선천성 심장 질환에서의 수술적 폐동맥 판막 치환술에 대한 고찰

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ABSTRACT

A study of surgical pulmonary valve replacement in congenital heart disease

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Objectives : The purpose of this study was to establish long-term survival data of surgical pulmonary valve replacement (PVR) in congenital heart disease (CHD) and to identify risk factors for mortality, in-hospital mortality, and repetitive PVR.

Methods : This is a retrospective study of 375 surgical PVR in 293 consecutive patients who underwent surgical PVR for CHD between January 2000 and May 2020. Conduit changes between the right ventricle and pulmonary artery were excluded from the analysis.

Results : The median age of the patients who underwent surgical PVR was 179 (range, 3-704)months. The mean age at first open-heart surgery was 12 months (0.1-177 months) and the mean age interval between first open-heart surgery and first PVR was 146 months (1-459 months). The mean follow-up duration was 23.5 years (0.1-41 years). There were 3 patients with in-hospital mortality (1.0%) and 15 patients with total mortality (5.1%) during follow-up. The survival rate was 95.1% over 25 years of follow-up period. Multivariate analysis demonstrated that more than three previous open-heart surgeries before surgical PVR (HR, 13.808; 95% CI, 3.507 54.363; P<0.001), age at the first operation (HR, 1.018; 95% CI, 1.000 1.036; P=0.046), longer duration of cardiopulmonary bypass(CPB)(HR, 1.009; 95% CI, 1.004 1.013; P<0.001) and longer duration of intensive care unit(ICU) stay (HR, 1.073; 95% CI, 1.043 1.104; P<0.001) were predictors for mortality following surgical PVR. Only CPB time (HR, 1.010; 95% CI, 1.006 1.014; P<0.001) was risk factor for in-hospital mortality after surgical PVR by multivariate analysis. The presence of multiple valve problems, duration of ICU stay, operation time, younger age and male sex were risk factors for redo PVR.

Conclusions : As the adult CHD population grows, redo PVR is inevitable and helpful for the patient with problems in pulmonary valve. Regardless of the successful long term survival rate of PVR, it should be performed with caution for those who previously underwent multiple open-heart surgeries, especially if the patient received more than 3 times of open-heart surgeries.

In addition, CPB time should be reduced during a surgery because longer CPB time was the only important risk factor for mortality and in-hospital mortality.

Keywords: Pulmonary valve replacement, mortality, in-hospital mortality, repetitive pulmonary valve replacement, risk factor analysis, childhood

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LIST OF ABBREVIATIONS

ACHD: Adult congenital heart disease

CHD: Congenital heart disease

TOF: Tetralogy of Fallot

DORV: Double-outlet right ventricle

RVOT: Right ventricular outflow tract

PVR: Pulmonary valve replacement

RV: Right ventricule

CPB: Cardiopulmonary bypass

ACC: Aortic cross-clamping

ICU: Intensive care unit

ECMO: Extracorporeal membrane oxygenation

INTRODUCTION

As the adult congenital heart disease(ACHD) population grows, the re-operation and long-term complications of previously corrected cardiac lesions have become evident.[1] Surgical palliation of many forms of complex congenital heart disease, including tetralogy of Fallot (TOF), double-outlet right ventricle (DORV), and transposition of the great arteries, commonly involves reconstruction of the right ventricular outflow tract (RVOT).[2] Pulmonary valve replacement(PVR) is the most common reoperation in ACHD and is often required as pulmonary insufficiency gradually progress at the previously corrected lesion.[3] Although the majority of patients with significant pulmonary regurgitation are asymptomatic for many years, they remain at risk for progressive right ventricular (RV) dilatation and reduced ventricular function, development of arrhythmia, or sudden death.[4] PVR in these patients has previously been demonstrated to significantly improve in RV function and exercise tolerance.[5,6]

Among the various valve substitutes for PVR, bioprosthetic valves are the most widely used because they are readily available and do not need permanent anticoagulation therapy in the low-pressure RV.[7] Several types of bioprosthetic valves have been used for surgical PVR, but all are prone to failure and will likely require reintervention.[8] Although surgical PVR with a bioprosthetic valve is the most commonly used technique for

RVOT reconstruction, surgical results with a bioprosthetic PVR and prognostic factors for CHD have not yet been clearly defined.

In this study, we aimed to establish long-term survival data of surgical PVR for CHD and to identify risk factors for mortality, in-hospital mortality, and repetitive PVR.

MATERIALS AND METHODS

Patients

We conducted a retrospective study of 375 surgical PVR in 293 consecutive patients who underwent surgical PVR for CHD in the Seoul National University Children's Hospital between January 2000 and May 2020. The previous surgical history of patients who underwent surgery during the study period was also included. Patients who underwent RV to pulmonary artery conduit change operation, and those who underwent single PVR without previous open heart surgery were excluded.

Data collection

Demographic, clinical, operative and imaging data were obtained from the patients' medical records. We collected data including patients' age, sex, diagnosis, prior procedures, comorbidities, type and size of valve, operation time, cardiopulmonary bypass (CPB) and aortic cross clamp (ACC) times, duration of intensive care unit (ICU) and hospital days. The type of implanted valve and other specifics of the surgical procedures were obtained from the operative reports. This study used clinical data retrieved from Seoul National University Hospital Patients Research Environment (SUPREME) system. This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB number: 1908-081-1054, approved date: Sep 6th, 2019).

The individual data linkage to mortality data was made under agreement between the National Health Insurance Service and Statistics Korea. After internal linkage processes in Statistics Korea, aggregate data without any personal identifiers were transferred to the researchers of this study for final analyses.

Definition and outcomes

Open heart surgery was defined as a surgery in which the thoracic cavity is opened to expose the heart and the blood is recirculated and oxygenated by a heart lung machine. Complex TOF was defined as TOF with other congenital structural malformation such as major aortopulmonary collateral artery, absent pulmonary valve or pulmonary atresia. In-hospital mortality was defined as death occurring during the hospital stay. Cardiac dysfunction was defined as patient who needs heart failure medication support even after 6 months of surgery.

The primary outcome of this study was patients' survival and risk factor for mortality or in-hospital mortality. The second outcome of this study was repetitive pulmonary valve replacement after previous pulmonary valve replacement and risk factor for repetitive PVR.

Data analysis

Data were expressed as median (range) or mean ± standard deviation (SD). Continuous variables were analyzed using Wilcoxon rank-sum test and discrete variables were analyzed using chi-square tests. To select candidate factors for independent variables to be included in the Cox model, the continuous variables were checked to determine if the proportional risk assumption was satisfied using restricted cubic splines. For categorical variables, the proportional risk assumption was confirmed by using a log-log(survival) plot or from the interaction with the time variable. Only the variables that satisfied the proportional risk assumption were analyzed.

Univariate and multivariate analysis, reported as odds ratios(ORs) with 95% confidence intervals(Cis), were carried out for risk factors of mortality and repetitive PVR. The survival rates of each group were compared using the log-rank test. As appropriate, $P < 0.05$ was considered statistically significant. All data analyses were performed using SAS (9.4 Version; SAS Institute Inc., Cary, NC, USA.)This study was supported by the Medical Research Collaborating Center at Seoul National

University College of Medicine and Seoul National University Hospital.

RESULTS

Patient characteristics

The demographic characteristics of the patients are described in Table 1. Overall, 293 patients were found to have undergone surgical PVR during the study period at a median age of 179 months (range, 3-704 months). The mean age of the patients at initial open-heart surgery was 12 months (range, 0.1-177 months) and the mean interval between initial open-heart surgery and first PVR was 146 months (range, 1-459 months). Of the total study participants, 99 were women (33.8%). The most common fundamental diagnosis was TOF (n=244, 83.3%); among which, 215 cases were simple TOF and 29 cases were complex TOF. The mean duration of ICU stay was 3 days (1-105 days), the mean hospital stay was 12 days (range, 4-148 days), and the mean follow-up duration was 23.5 years (range, 0.1-41 years).

Table 1. Demographic characteristics of the patients

Male/Female	194/99
Fundamental diagnosis	
Simple TOF	215
Complex TOF	29
TGA	16
DORV	16
Congenital valve malformation	8
Others	9
Associated syndrome	
CATCH 22	16
Age at PVR, months (range)	179 (3−704)
Age at initial open−heart surgery, months(range)	12 (0.1−177)
Interval between initial open−heart surgery and 1st PVR, months (range)	146 (1−459)
Duration of ICU stay, days (range)	3 (1−105)
Duration of hospital stay, days (range)	12 (4−148)
Follow up duration, years (range)	23.5 (0.1−41)

Continuous variables are described as median and ranges. TOF: Tetralogy of Fallot, DORV: Double outlet right ventricle, TGA: Transposition of great arteries, PVR: Pulmonary valve replacement, ICU:Intensive care unit

Surgical pulmonary valve replacement

The surgical PVR data are summarized in Table 2. PVR was performed through a median sternotomy on cardiopulmonary bypass with mild hypothermia. Aortic cross-clamping is dependent on the surgeon's preference or concomitant procedures. The median operation time was 385 min (range, 57–1015 min), the median CPB time was 152 min (range, 47–682 min), and the median ACC time was 44 min (range, 0–287 min). The choice of prosthetic pulmonary valve was at the discretion of the surgeon. The most commonly used valve was the tissue valve (n=368, 98.1%), and among them, the stented bioprosthetic porcine valve was the most commonly used valve (n=270, 73.4%). The most commonly performed concomitant procedure was right ventricular outflow tract surgery or pulmonary artery angioplasty (n=261, 69.6%).

Table 2. Surgical pulmonary valve replacement data

Operation time (min)	385 (57–1015)
CPB time (min)	152 (47–682)
ACC time (min)	44 (0–287)
Type of prosthetic pulmonary valve*	
Mechanical	7
Tissue	368
Stented porcine valve	270
Stented bovine pericardial valve	74
PTFE bicuspid valve	8
Homograft	5
Stentless porcine valve	3
Others	8
Size of prosthetic pulmonary valve	
Mechanical (mm)	25 (23–27)
Tissue (mm)	25 (12–29)
Concomitant procedures	
RVOT operation or pulmonary artery angioplasty	261
TVP or TAP or TVR	71
Residual ASD or VSD closure	29
Right side cryoablation	28

AVP or AVR	13
Pacemaker insertion	7
Vegetation removal or thrombus removal	7
MVP or MAP or MVR	5
Arch repair	2
Others	9

Continuous variables are described as medians ad ranges. CPB: Cardiopulmonary bypass, ACC: Aortic cross-clamping, PVR: Pulmonary valve replacement, RVOT: Right ventricular outflow tract, TVP: Tricuspid valvuloplasty, TAP: Tricuspid annuloplasty, TVR: Tricuspid valve replacement, ASD: Atrial septal defect, VSD: Ventricular septal defect, AVP: Aortic valvuloplasty, AVR: Aortic valve replacement, MVP: Mitral valvuloplasty, MAP: Mitral annuloplasty, MVR: Mitral valve replacement

Follow-up outcomes and comorbidity

The outcomes and comorbidities of surgical pulmonary valve replacement are summarized in Table 3. There were 3 patients with in-hospital mortality and 15 patients with total mortality during follow-up. The survival rate was 95.1% over a 25-year follow-up period. (Figure 1) There were 89 re-interventions, of which 80 were surgical PVR and 9 were percutaneous PVR. Seventy-four patients (74/293, 25.3%) had pre- and postoperative comorbidities. Twenty-two patients (22/74, 29.7%) had multiple comorbidities, the most common of which was liver disease (18/74, 24.3%).

The characteristics of the patients with in-hospital mortality are summarized in Table 4. Patient 1 was a 24-year-old male with a fundamental diagnosis of TOF who underwent second redo PVR due to pulmonary regurgitation and pulmonary stenosis aggravation. During the dissection, the ascending aorta was torn due to severe adhesion, and excessive bleeding occurred as a result. After the operation, he could not be weaned from CPB and underwent central extracorporeal membrane oxygenation(ECMO) support. He died of excessive postoperative bleeding, which resulted in multi-organ failure. Patient 2 was a 19-year-old woman with a fundamental diagnosis of DORV who had previously undergone open heart surgery 4 times. She underwent a second redo PVR due to prosthetic valve failure. During the dissection, the aorta and RA free wall ruptured due to severe adhesion, and massive bleeding occurred at the right ventricle to the pulmonary artery anastomosis site. After the operation, she could not be weaned from CPB and underwent central ECMO support. She died of excessive postoperative bleeding and disseminated intravascular coagulation. Patient 3 was a 23-year old woman with a fundamental diagnosis of TOF with absent pulmonary valve syndrome. She underwent redo PVR because of homograft failure. There were no intraoperative events, but she suffered convulsions on the 2^{nd} day after surgery, and diffuse brain damage was confirmed by brain magnetic resonance imaging and electroencephalogram. She died on the 103^{rd} day after the operation due to disseminated intravascular coagulation, resulting in massive oral and nasal bleeding and multi-organ failure.

Table 3. Outcomes and comorbidity for surgical pulmonary valve replacement

Primary outcome	
Total mortality	15
In−hospital mortality	3
Second outcome	
Surgical re−do PVR	80
Percutaneous re−do PVR	9
Morbidity	
None, n(%)	219/293(74.7)
Multiple comorbidities, n(%)	22/74(29.7)
Liver, n(%)	18/74(24.3)
Endocrine, n(%)	14/74(18.9)
Brain, n(%)	13/74(17.6)
Kidney, n(%)	10/74(13.5)
Lung, n(%)	8/74(10.8)
Psychotic problem, n(%)	7/74(9.5)
Haemato−oncologic problem, n(%)	5/74(6.8)
Other, n(%)	23/74(31.1)

PVR: pulmonary valve replacement

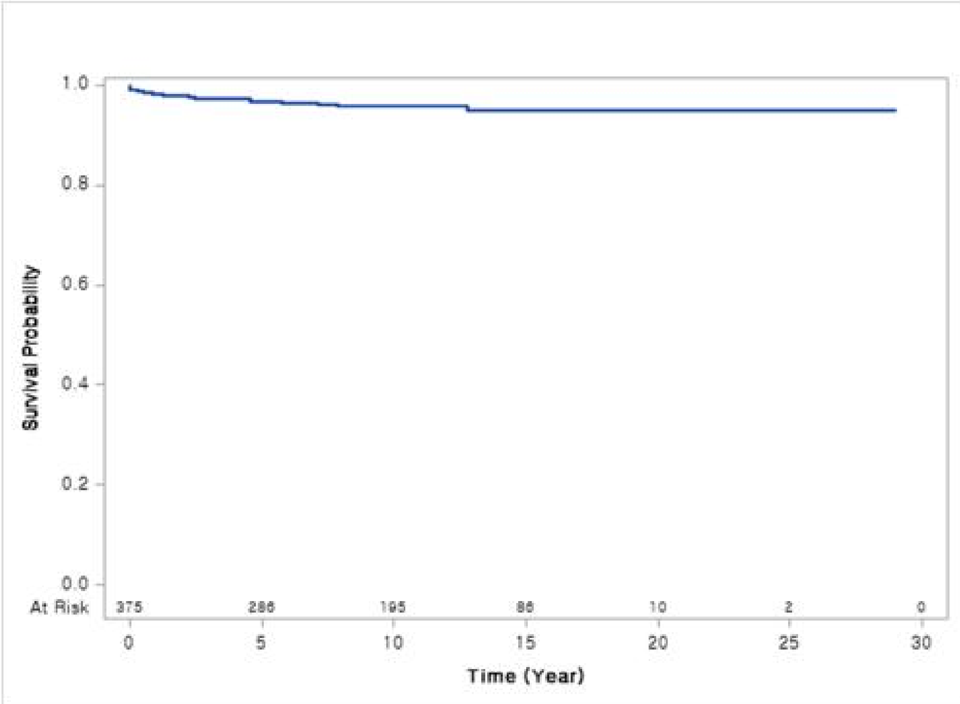

Figure 1. Overall survival from surgical pulmonary valve replacement. The survival rate after 25 years of follow-up was 95.1%

Table 4. Patient characteristics of in−hospital mortality

	Patient 1	Patient 2	Patient 3
Age (years)	24	19	23
Sex	Male	Female	Female
Fundamental diagnosis	TOF	DORV	TOF absent pulmonary valve syndrome
Previous OHS number	2	4	2
Cause of re−operation	PR and PS aggravation	Prosthetic valve failure	Homograft failure
CPB weaning	No	No	Yes
Central ECMO support	Yes	Yes	Yes
Bleeding control operation	No	Yes	No
Intra−operation event	Ascending aorta tear	Aorta, RA free wall rupture during dissection Massive bleeding from RV−PA anastomosis site	None
Cause of death	Excessive post−operative bleeding Multi−organ failure	Excessive post operative bleeding Disseminated intravascular coagulation	Postoperative diffuse brain damage Disseminated intravascular coagulation
Time of death	POD # 3	POD #12	POD #103

TOF: Tetralogy of Fallot, DORV: Double-outlet right ventricle, OHS: Open heart surgery, PR: Pulmonary regurgitation, PS: Pulmonary stenosis, CPB: Cardiopulmonary bypass, ECMO: Extracorporeal membrane oxygenation, RA: Right atrium, RV: Right ventricle, PA: Pulmonary artery, POD: Post operative day

Prognostic factors for mortality of surgical pulmonary valve replacement

The characteristics of both patients and valves were assessed as potential prognostic factors for mortality of surgical PVR and are summarized in Table 5. Statistically significant variables at the 20% significance level in the univariate analysis, were selected as independent variables to be included in the multivariate analysis. Univariate analysis showed that the presence of comorbidity or multiple comorbidities, number of prior open-heart surgeries before PVR, multiple valve problems, cardiac dysfunction, duration of hospital and ICU stay, emergency operation, operation time, CPB time, ACC time, prolonged postoperative inotropic support, and use of mechanical valve were associated with mortality. Multivariate analysis demonstrated that prior open-heart surgery at least 3 times before PVR (HR, 13.808; 95% CI, 3.507-54.363; P<0.001), age at the 1st operation (HR 1.018; 95% CI, 1.000-1.036; P=0.046), longer duration of CPB (HR, 1.009; 95% CI, 1.004-1.013; P<0.001) and duration of ICU stay (HR, 1.073; 95% CI, 1.043-1.104; P<0.001) were predictors of mortality from surgical PVR.

Patients who previously underwent multiple PVR and open-heart surgeries had significantly higher mortality rates. The mortality rate increased with the number of PVR surgeries. (P<0.001, Fig 2A) Patients who underwent surgical PVR after at least three previous open-heart surgeries had significantly higher mortality than those who underwent PVR with less than three. ($P<0.001$, Fig 2B)

Table 5. Prognostic factors analysis for mortality of surgical pulmonary valve replacement

Characteristic		Univariate analysis HR(95% CI)	P	Multivariate analysis HR (95% CI)	P
Age at PVR		1.004(0.999 - 1.008)	0.111		
Sex	Male (Ref)				
	Female	0.541 (0.153−1.918)	0.342		
Simple Tetralogy of Fallot	No (Ref)				
	Simple TOF	0.454 (0.165−1.252)	0.127		
Simple PVR	No (Ref)				
	Simple PVR	0.362 (0.048−2.756)	0.327		
Associated comorbidity	No(Ref)				
	Yes	3.322(1.204−9.163)	0.020*		
Multiple comorbidities	No(Ref)				
	Yes	5.557(1.898−16.269)	0.002*		
No. of prior open−heart surgeries before PVR	<3(Ref)				
	≥3	7.713(2.757−22.139)	<0.001*	13.808(3.507−54.363)	<0.001†
Multiple valve problems	No(Ref)				
	Yes	3.421(1.240−9.434)	0.018*		
Pre−operation LV dysfunction	LV EF ≥50% (Ref)				
	LV EF	1.346(0.165−10.949)	0.781		

	<50%				
Cardiac dysfunction	No (Ref)				
	Yes	19.89(4.487−88.155)	<0.001*		
Pre−operation arrhythmia	No(Ref)				
	Yes	2.606(0.945−7.190)	0.064		
Operation era	Before 2010(Ref)				
	After 2010	1.177(0.401−3.452)	0.766		
1^{st} operation age		1.011(0.995−1.029)	0.181	1.018(1.000−1.036)	0.046†
1^{st} operation − 1^{st} PVR interval		1.001(0.994−1.007)	0.881		
Duration of hospital stay		1.033(1.020−1.047)	<0.001*		
Duration of ICU stay		1.052(1.031−1.073)	<0.001*	1.073(1.043−1.104)	<0.001†
Emergency operation	No(Ref)				
	Yes	19.20(2.45−150.37)	0.005*		
Operation time		1.008(1.005−1.011)	<0.001*		
CPB time		1.010(1.006−1.014)	<0.001*	1.009(1.004−1.013)	<0.001†
ACC time		1.009(1.003−1.016)	0.007*		
Post operation prolonged inotropics support	< 7 days(Ref)				
	≥7 days	13.31(4.468−39.649)	<0.001*		
Mechanical valve	Tissue				

	valve (Ref)		
	Mechanical valve	9.136 (2.059–40.532)	0.004*

PVR: Pulmonary valve replacement, ICU: Intensive care unit, LV: Left ventricle, CPB: Cardiopulmonary bypass, ACC: Aortic cross–clamp

* Significant univariate association

† Significant independent risk factors for mortality due to surgical pulmonary valve replacement by multivariate analysis

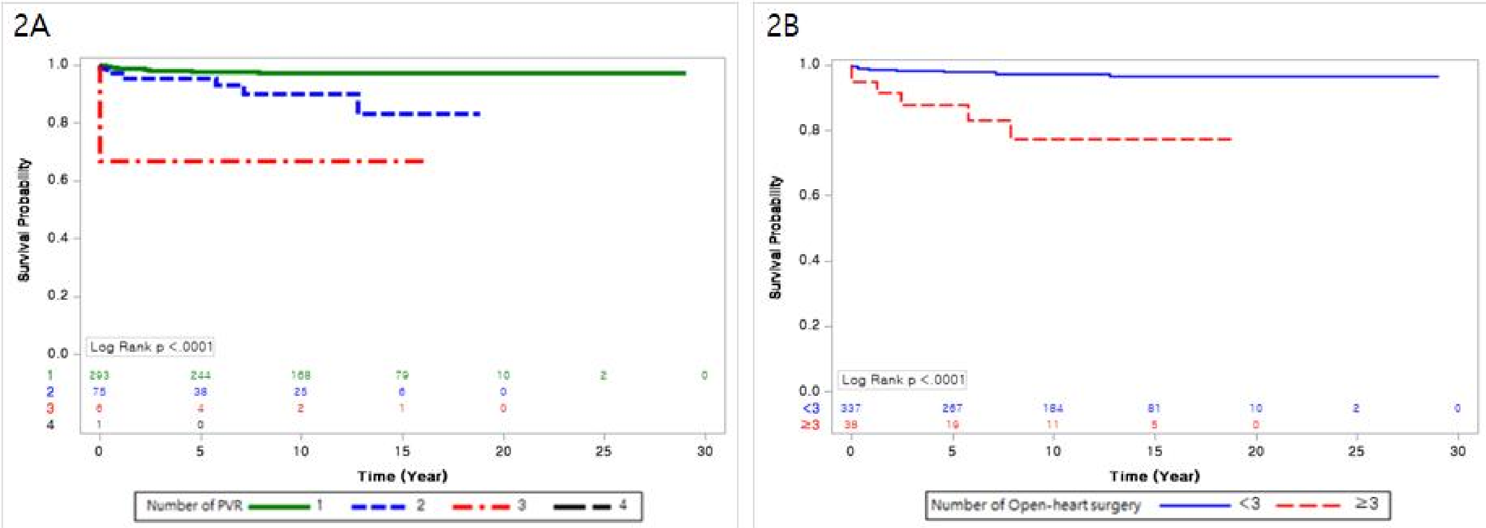

Figure 2. Log rank analysis of mortality after surgical PVR stratified by number of PVR (2A) and number of open−heart surgeries (2B). The mortality rate increased with the number of PVR surgeries.(P<0.001) In addition, patients who underwent PVR after three or more previous open−heart surgeries had significantly higher mortality than those undergoing PVR with less than three. (P<0.001)

PVR: Pulmonary valve replacement

Subgroup analysis between simple TOF and others

Simple TOF was not a significant factor for mortality in surgical PVR. However, when we performed subgroup analysis between simple TOF and others (summarized in Table 6) the duration of ICU stay and CPB time were significantly longer and the rate of cardiac dysfunction was significantly higher in the deceased patients of both groups.

Table 6. Subgroup analysis between the simple tetralogy of Fallot group and the others group

	Simple TOF group			Others		
	Death (n=7)	Survive (n=243)	P value	Death (n=8)	Survive (n=117)	P value
Hospital stay(days)	24(5–107)	11(4–106)	0.250	20(9–148)	14(5–82)	0.024
ICU stay (days)	5(3–105)	3(0–47)	0.002	10(3–19)	3(0–40)	0.001
CPB time (min)	242(82–384)	145(0–462)	0.030	252(143–682)	168(0–489)	0.013
Comorbidity	57%(4/7)	25%(61/243)	0.077	50%(4/8)	24%(28/117)	0.202
Multiple comorbidities	43%(3/7)	9%(22/243)	0.024	25%(2/8)	4%(5/117)	0.064
Number of open heart surgery before PVR (≥3)	29%(2/7)	7%(16/243)	0.083	50%(4/8)	14%(16/117)	0.022
Heart dysfunction	86%(6/7)	20%(49/243)	0.001	88%(7/8)	28%(33/117)	0.001
Post–op inotropic support (≥7 days)	17%(1/7)	3%(7/243)	0.185	63%(5/8)	9%(11/117)	<0.001
Mechanical valve	0%(0/7)	1%(3/243)	1.000	25%(2/8)	2%(2/117)	0.020

TOF: Tetralogy of Fallot, ICU: Intensive care unit, CPB: Cardiopulmonary bypass, PVR: Pulmonary valve replacement, OP: Operation

Prognostic factors for in-hospital mortality of surgical pulmonary valve replacement

We additionally performed univariate and multivariate analyses to evaluate the prognostic factors for in-hospital mortality. The same factors as those used to evaluate hospital mortality were assessed as potential prognostic factors for in-hospital mortality of surgical PVR and are summarized in Table 7. Statistically significant variables at the 20% significance level in the univariate analysis, were selected as independent variables to be included in the multivariate analysis. Univariate analysis showed that duration of hospital day and ICU stay day, duration of operation, CPB time, ACC time, and prolonged postoperative inotropic support were associated with mortality. However, only CPB time (HR, 1.012; 95% CI, 1.006-1.018; P<0.001) was a risk factor for in-hospital mortality after surgical PVR by multivariate analysis.

Table 7. Prognostic factors analysis for in-hospital mortality of surgical pulmonary valve replacement

Characteristic		Univariate analysis		Multivariate analysis	
		HR(95% CI)	P-value	HR (95% CI)	P-value
Age at PVR		1.005(0.997-1.013)	0.253		
Sex	Male (Ref)				
	Female	1.102(0.100-12.152)	0.937		
Simple Tetralogy of Fallot	No (Ref)				
	Simple TOF	1.010(0.092-11.133)	0.994		
Simple PVR§	No (Ref)				
	Simple PVR	0.801(0.026-24.518)	0.899		
Associated comorbidity	No(Ref)				
	Yes	1.450(1.131-15.986)	0.762		
Multiple comorbidities	No(Ref)				
	Yes	5.561(0.504-61.346)	0.161		
No. of prior open-heart surgeries before PVR	<3(Ref)				
	≥3	4.570(0.414-50.413)	0.215		
Multiple valve problem	No(Ref)				
	Yes	7.956(0.721-87.746)	0.090		
Pre-operation LV	LV EF≥50%(Ref)				

dysfunction§	LV EF <50%	1.333(0.043−40.845)	0.869		
Cardiac dysfunction§	No (Ref)				
	Yes	21.19(0.69−648.70)	0.080		
Pre−operation arrhythmia	No(Ref)				
	Yes	5.556(0.504−61.282)	0.162		
Operation era§	Before 2010(Ref)				
	After 2010	21.856(0.70−679.76)	0.079		
1st Operation age		0.901(0.750−1.082)	0.265		
1st Operation − 1st PVR interval		1.001(0.987−1.014)	0.929		
Duration of hospital day		1.030(1.006−1.055)	<0.015*		
Duration of ICU stay day		1.054(1.029−1.079)	<0.001*		
Operation time		1.011(1.005−1.016)	<0.001*		
CPB time		1.012(1.006−1.018)	<0.001*	1.01(1.006−1.018)†	<0.001
ACC time		1.019(1.003−1.035)	0.018*		
Post operation prolonged inotropics support	< 7 days(Ref)				
	≥7 days	28.061(2.54−309.48)	<0.007*		
Mechanical valve§	Tissue valve(Ref)				
	Mechanical valve	7.438(0.24−227.88)	0.251		

PVR: Pulmonary valve replacement, ICU: Intensive care unit, LV: Left ventricle, CPB: Cardiopulmonary bypass, ACC: Aortic cross−clamp

* Significant univariate association

† Significant independent risk factors for in−hospital mortality due to surgical pulmonary valve replacement by multivariate analysis.

§Firth correction

Prognostic factors for repetitive pulmonary valve replacement

The potential prognostic factors for repetitive PVR are summarized in Table 8. In univariate analysis, statistically significant variables at the 20% significance level were selected as independent variables to be included in the multivariate analysis. Univariate analysis showed that younger age, male sex, 1st operation to 1st PVR interval, multiple valve problems, duration of ICU stay were associated with repetitive PVR. Age younger than 10 years, male, had multiple valve problems(HR, 1.883; 95% CI, 1.072-3.306; P=0.028) and duration of ICU stay (HR 1.048; 95% CI, 1.014-1.083; P=0.005) were predictors for repetitive PVR by multivariate analysis.

We performed additional subgroup analysis for the groups with and without multiple-valve problems and the results are summarized in Table 9. Patients with multiple valve problems had more multiple comorbidities, cardiac dysfunction, and a higher mechanical valve rate, but less simple TOF and single PVR than patients with a single valve problem. In addition, patients with multiple valve problems were younger and had a shorter 1st operation to PVR interval, longer hospital and ICU stay, operation time, CPB time, and AC time than patients with a single valve problem.

There were 80 surgical redo PVRs and 9 percutaneous re-do PVRs. Repetitive PVR was examined by dividing the patients into three groups by age < 10 years, 10−14 years, and ≥15 years. The group aged < 10 years had a higher incidence of repeat PVR. ($P<0.001$, Fig 3)

Table 8. Prognostic factors analysis for repeat pulmonary valve replacement

Characteristic		Univariate analysis HR(95% CI)	P	Multivariate analysis HR (95% CI)	P
Age		0.989 (0.985−0.992)	<0.001*		
Age grade	< 10years (Ref)				
	10−15years	0.331 (0.206−0.533)	<0.001*	0.398(0.232−0.684)	0.001†
	>15years	0.124 (0.062−0.250)	<0.001*	0.169(0.077−0.368)	<0.001†
1st Operation age		0.995(0.983−1.008)	0.450		
Operation era	Before 2010(Ref)				
	After 2010	0.605(0.287−1.277)	0.187		
Sex	Male(Ref)				
	Female	0.385 (0.218−0.678)	0.001*	0.245(0.115−0.524)	<0.001†
1st Operation − 1st PVR interval		0.991(0.987−0.994)	<0.001*		
Simple Tetralogy of Fallot	No (Ref)				
	Simple TOF	0.824(0.525−1.294)	0.401		
Simple PVR	No (Ref)				
	Simple PVR	1.136(0.646−1.998)	0.657		
Associated comorbidity	No(Ref)				
	Yes	0.975(0.598−1.589)	0.918		
Multiple	No(Ref)				
	Yes	1.702(0.876−3.307)	0.117		

comorbidity					
No. of prior open−heart surgeries before PVR	<3(Ref)				
	≥3	1.183(0.513−2.732)	0.693		
Multiple valve problems	No(Ref)				
	Yes	1.727 (1.055−2.827)	0.030*	1.883(1.072−3.306)	0.028†
Pre−operation LV dysfunction	LV EF ≥50% (Ref)				
	LV EF <50%	0.811 (0.241−2.729)	0.736		
Cardiac dysfunction	No (Ref)				
	Yes	1.286 (0.801−2.064)	0.298		
Pre−operation arrhythmia	No(Ref)				
	Yes	1.236(0.757−2.018)	0.398		
Duration of hospital stay		1.005(0.991−1.020)	0.498		
Duration of ICU stay		1.043(1.010−1.078)	0.010*	1.048(1.014−1.083)	0.005†
CPB time		1.000(0.997−1.003)	0.981		
ACC time		1.000(0.995−1.005)	0.951		
Post operative	< 7 days(Ref)				
		1.418(0.569−3.537)	0.454		

prolonged inotropic support	≥7 days		
Mechanical valve	Tissue valve(Ref)		
	Mechanical valve	0.258(0.016−4.270)	0.344

PVR: Pulmonary valve replacement, ICU: Intensive care unit, LV: Left ventricle, CPB: Cardiopulmonary bypass, ACC: Aortic cross−clamp

* Significant univariate association

† Significant independent risk factors for repetitive surgical pulmonary valve replacement by multivariate analysis.

Table 9. Comparison between the multiple valve problem group and the single valve problem group

	Multiple(n=76)	Single (n=299)	P value
Age (months)	152.5(3−477)	182(7−704)	0.012
1st op Age(months)	13(0.2−118)	12(0.1−177)	0.638
1st op - PVR interval (months)	111(1−371)	148(2−459)	<0.001
Hospital stay(days)	14(6−148)	12(4−107)	0.001
ICU stay (days)	3(1−47)	3(0−105)	0.001
Operation time(min)	435(225−1015)	380(57−845)	<0.001
CPB time (min)	179(78−682)	147(0−489)	<0.001
ACC time (min)	86(0−287)	25(0−249)	<0.001
Sex (female)	29%(22/76)	31%(94/299)	0.675
Simple TOF	46%(35/76)	72%(215/299)	<0.001
Simple PVR	3%(2/76)	18%(53/290)	0.001
Comorbidity	34%(26/76)	24%(71/299)	0.063
Multiple comorbidities	20%(15/76)	6%(17/299)	<0.001
Number of open heart surgeries before PVR (≥3)	14%(11/76)	9%(27/299)	0.160
Pre−op LV dysfunction (EF <50%)	10%(5/49)	10%(22/223)	1.000
Heart dysfunction	37%(28/76)	22%(67/299)	0.010
Arrhythmia	33%(25/75)	25%(75/296)	0.163
Emergency operation	1%(1/73)	1%(2/290)	0.491

Post op inotropic support (≥7 days)	12%(9/73)	5%(15/286)	0.061
Mechanical valve	7%(5/76)	1%(2/299)	0.005

OP: Operation, PVR: Pulmonary valve replacement, ICU: Intensive care unit, LV: Left ventricle, CPB: Cardiopulmonary bypass, ACC: Aortic cross-clamp, TOF: Tetralogy of Fallot

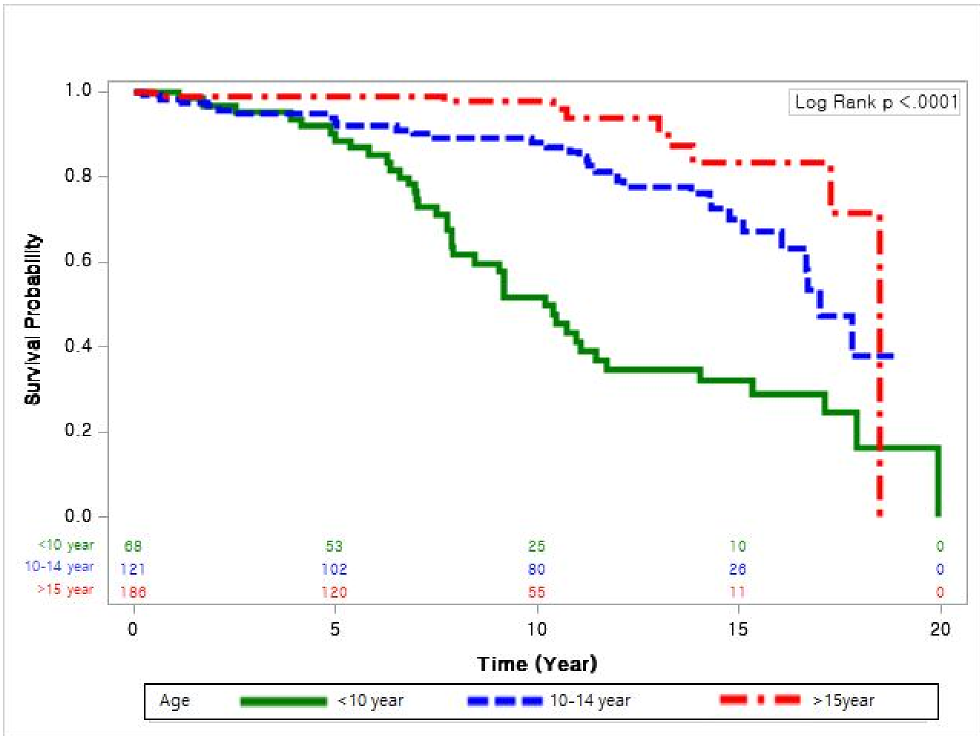

Figure 3. Log rank test of redo PVR after repeat surgical PVR. The repeat PVR was examined by dividing the patients into three groups by age: < 10 years, 10−14 years, and ≥15 years. The < 10 years group had a higher incidence of repetitive PVR. (P<0.001)

Comparison of long-term durability between the stented porcine group and the stented bovine group

The most commonly used valve was the tissue valve (n=368, 98.1%). A stented bioprosthetic porcine valve (n=270, 73.4%) was the most commonly used valve among them, followed by the stented bovine pericardial valve (n=74, 20.1%). A log-rank test was performed to compare the differences in repetitive PVR rates between two groups. Compared with the stented bovine pericardial valve, the porcine valve had long-term advantages in terms of reduced reoperation rate(Figure 4).

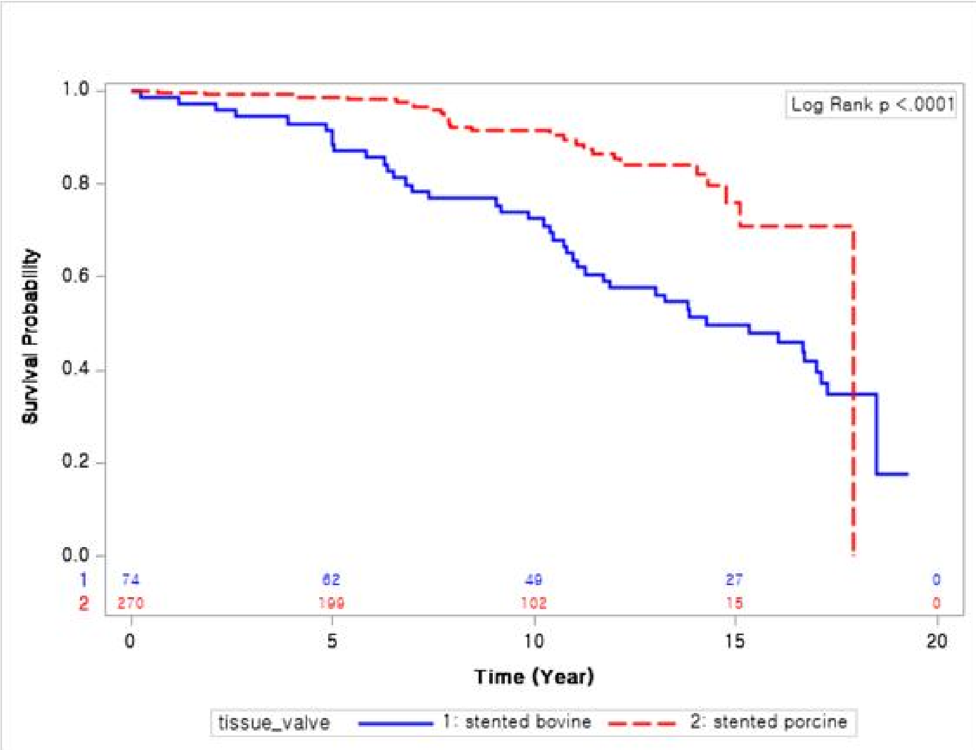

Figure 4. Log rank test of redo PVR in the stented porcine group and stented bovine group. The rate of reoperation was significantly higher in the stented bovine group. (P<0.001)

DISCUSSION

As the adult congenital heart disease population grows, it is becoming increasingly important to identify patients at the greatest risk for mortality and repeat operations. PVR is a frequently performed procedure in the field of congenital heart surgery and is the most common cardiac operation and reoperation performed in adults with CHD. [3] [9] Our study primarily focused on determining the outcome and potential risk factors contributing to mortality and repeat PVR after surgical PVR. This study showed good operative outcomes (95.1% survival rate over a follow-up period of 25 years) although there were 3 in-hospital mortalities. To the best of our knowledge, this is the first study to show the risk factors for mortality and redo PVR after surgical PVR in CHD.

The number of prior open-heart surgeries, age at the 1st operation, duration of ICU stay, and CPB time were risk factors for mortality after surgical PVR. However, only CPB time was a risk factor for in-hospital mortality after surgical PVR by multivariate analysis. In addition, the presence of multiple valve problems, duration of ICU stay, younger age, and male sex were risk factors for redo PVR.

In our study, an increase in the number of prior open-heart surgeries was one of the main risk factors for mortality due to repeat surgical PVR. This might be related to repeat sternotomies and repeat open-heart surgeries increase the difficulty of surgery and CPB time. Although the Texas Children's Hospital reported excellent results on repeat sternotomy in congenital heart surgery and concluded that repeat sternotomy was no longer a risk factor for morbidity or mortality[10], other groups have reported that an increase in the number of sternotomies was associated with an increase in operative mortality.[9,11,12] In addition, Giamberti et al.[13], in their study of 164 adults with congenital heart disease who underwent cardiac reoperations, reported that postoperative morbidity was associated with the number of previous operations. The median number of previous open-heart operations for mortality cases in our study (n=15) was 2 (range, 1-5).

Patients with adverse events had a significantly longer duration of ICU stay. It is common finding in the literature and self-explanatory that the occurrence of postoperative complications after congenital heart surgery is associated with prolonged ICU stay.[14] We also found that mortality and in-hospital mortality after PVR was associated with longer CPB time, although most cases of mortality were noted more than 30 days after PVR in our study. Longer CPB time is a well-known independent risk factor for postoperative complications after congenital heart surgery[13,15,16]. In the case of performing concomitant operation as well as simple PVR, the CPB time was longer. This means that the difficulty of the surgery increases and may be related with an increase in mortality.

We performed subgroup analysis between the simple TOF group and the other group. In both groups, the cardiac dysfunction rate was higher in deceased patients, indicating that clinicians should be more alert when treating patients with cardiac dysfunction after surgery.

Simple PVR was not a statistically significant risk factor for in-hospital mortality. However, among patients who received simple PVR, none showed in-hospital mortality. This is possibly due to the small number of in-hospital mortality cases (n=3). We hope that further studies will reveal the relationship between simple PVR and in-hospital mortality.

The presence of multiple valve problems was associated with repeat PVR in both univariate and multivariate analyses. The most commonly involved valve was the tricuspid valve. This might be related to more severe hemodynamic interactions between valve lesions in patients with multiple valve problems and this hemodynamic burden seems to also affect the durability of the replaced valve. In addition, patients with multiple valve problems were younger and had more multiple comorbidities, heart dysfunction, and mechanical valves, but less simple TOF and single PVR than patients with single valve problem. This indicates that patients in the multiple valve problem group had more severe disease than those in the single valve problem group.

We performed subgroup analysis between the stented porcine group and the stented bovine group to compare the difference in repetitive PVR rates. Compared with the stented bovine valve, the stented porcine valve had long-term advantages in terms of reduced reoperation rates. This resut is in agreement with the findings of previously published data.[17]

To improve long-term outcomes of PVR, percutaneous pulmonary valve implantation has recently emerged as an alternative treatment option for failed bioprosthetic valves.[18] In addition, the multicenter United States Melody Valve trial[19] showed a high rate of procedural success and good clinical outcome. This technique is expected to reduce the number of operations during the lifetime of patients who have undergone bioprosthetic PVR.

The present study was limited by its retrospective nature. In addition, statistical significance is likely to be reduced as a result of the insufficient number of patients with mortality, especially in-hospital mortality.

In conclusion, as the adult CHD population grows, redo PVR is inevitable and helpful for the patient with problems in pulmonary valve. Regardless of the successful long term survival rate of PVR, it should be performed with caution for those who previously underwent multiple open-heart surgeries, especially if the patient received more than 3 times of open-heart surgeries. In addition, CPB time should be reduced during a surgery because longer CPB time was the only important risk factor for mortality and in-hospital mortality.

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국문 초록

목적: 이 연구의 목적은 선천성 심장 질환에서의 수술적 폐동맥 판막 치환술의 치료 성적과 사망 및 반복적인 폐동맥판막 치환술에 기여하는 위험인자들을 조사하는 것이다.

방법: 2000년 1월부터 2020년 5월까지 서울대학교 어린이 병원에서 선천성 심장 질환으로 인하여 폐동맥판막 치환수술을 받은 293명의 환자 및 375건의 수술을 대상으로 후향적 연구를 시행하였다. 우심실과 폐동맥 사이의 도관 교체는 본 연구에서 제외하였다.

결과: 폐동맥 판막 치환 수술을 받은 평균 연령은 179개월(3-704개월) 이었다. 첫 번째 개흉술을 받은 나이는 평균 12개월(0.1-177개월) 이었으며, 처음 시행 받은 개흉술과 폐동맥판막 치환 수술 간의 간격은 평균 146개월(1-459개월) 이었다. 평균 추적 기간은 23.5년(1-41년) 이었다. 4명의(1.4%) 환자들이 수술 후 퇴원하지 못하고 사망하였으며, 추적 기간 중 총 15명의 (5.1%) 환자들이 사망하였다. 25년 동안의 추적 관찰 동안 생존률은 95.1% 였다. 다변량 분석 결과 폐동맥판막 치환 수술 전 개흉술 횟수가 3번 이상인 경우 (위험비 13.808 95% 신뢰구간 3.507-54.363; P<0.001), 첫 수술시 연령 (위험비 1.018 95% 신뢰구간 1.000-1.036; P=0.046), 체외 순환기 시간 (위험비 1.009 95% 신뢰구간 1.004-1.013; P<0.001), 중환자실 재원 기간 (위험비 1.073 95% 신뢰구간 1.043-1.104; P<0.001) 이 폐동맥 판막 치환 수술의 사망률을 예측하는 인자였다. 그리고 체외 순환기 시간 (위험비 1.010 95% 신뢰구간 1.006-1.014; P<0.001)만이 폐동맥 판막 치환 수술 이

후 원내 사망률을 예측하는 유일한 인자였다. 단변수 및 다변수 분석 결과 두 개 이상의 판막에 문제 있는 경우, 중환자실 재원 기간과 수술 시간이 길수록, 수술 시 나이가 어릴수록, 남자가 재수술을 예측하는 인자였다.

결론: 성인 선천성 심장병 환자들이 증가함에 따라 폐동맥 판막에 질환이 있는 환자들에게 수술적 폐동맥 판막 피환술을 받는 것은 불가피하며 도움이 되는 수술이다. 수술적 폐동맥 판막 치환술은 좋은 장기 수술 성적을 보이고 있으나, 반복적인 수술 시 사망률과 반복적 수술의 위험인자를 밝히는 것은 매우 중요하며, 3번 이상의 개흉술을 받은 경우에는 사망률 및 수술 후 병원 내 사망률이 높아 주의를 요한다. 또한, 장기간의 체외순환기 시간이 사망률의 유일한 중요한 위험 요소이기에 수술적 폐동맥 판막 치환술 시 체외 순환기 시간을 줄이기 위한 노력을 하여야 한다.

주요어: 폐동맥 판막 치환술, 사망률, 병원 내 사망, 반복적인 폐동맥 판막 치환술, 위험인자, 소아기

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