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Outcomes of Reoperative Valve Replacement in Patients with Prosthetic Valve Endocarditis: A 20-Year Experience

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Background: Prosthetic valve endocarditis (PVE) is a serious complication of cardiac valve replacement, and many patients with PVE require reoperation. The aim of this study was to review our institutional 20-year experience of surgical reoperative valve replacement in patients with PVE. **Methods:** A retrospective study was performed on 84 patients (mean age, 54.8±12.7 years; 51 males) who were diagnosed with PVE and underwent reoperative valve replacement from January 1995 to December 2016. **Results:** PVE was found in 1 valve in 61 cases (72.6%), and in 2 or more valves in 23 cases (27.4%). The median follow-up duration was 47.3 months (range, 0 to 250 months). Postoperative complications occurred in 39 patients (46.4%). Reinfection occurred in 6 cases, all within 1 year. The freedom from reinfection rate at 5 years was 91.0%±3.5%. The overall survival rates at 5 and 10 years were 64.4%±5.8% and 54.3%±7.3%, respectively. In stepwise multivariable Cox proportional hazard models, older age (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.05 to 2.10; p=0.027) and cardiopulmonary bypass (CPB) time (HR, 1.03; 95% CI, 1.00 to 1.01; p=0.033) emerged as independent risk factors for death. **Conclusion:** Older age and a longer CPB time were associated with an increased risk of overall mortality in PVE patients.

Key words: 1. Prosthesis
2. Endocarditis
3. Reoperation
4. Replacement

Introduction

Prosthetic valve endocarditis (PVE) is a serious complication of cardiac valve replacement, posing significant risks of mortality and morbidity. According to previous studies, PVE has been reported to occur with an incidence rate of 0.98 per 100 patient-years among patients who have undergone valve replacement surgery [1], and the cumulative incidence rates at 5 and 10 years have been reported to be 3% and 5%, respectively [2].

The optimal treatment strategy for PVE is still debated; some patients may sufficiently recover with medical treatment [3], but many patients require surgical replacement of the infected prosthesis [4]. Moreover, PVE is frequently hemodynamically unstable compared with native valve endocarditis (NVE), and surgery is often performed in an urgent or emergency setting. The surgical treatment of PVE tends to require longer cardiopulmonary bypass (CPB) times than operations for NVE due to the extensive adhesions from previous surgery [5] and the

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requirement for extensive debridement. Consequently, the PVE operative mortality rate has been reported to range from 20% to 65% [6]. However, in light of advancements in surgical techniques and perioperative care, the operative outcomes need to be re-evaluated in contemporary settings.

The aim of this study was to present an up-to-date analysis of our institutional experience of the surgical outcomes of reoperative valve replacement in PVE patients and to identify risk factors predictive of the prognosis.

Methods

1) Patients

We performed a retrospective review of consecutive patients who underwent reoperative valve replacement for PVE between January 1995 and December 2016 at Asan Medical Center, in Seoul, South Korea. We identified 84 patients (51 male) with a mean age of 54.8±12.7 years. Among them, 9 (10.7%) presented with early PVE (onset $<$60 days after insertion of prosthesis), while 75 (89.3%) presented with late PVE (onset $\geq$60 days after insertion of prosthesis). The database included the baseline patient characteristics; further detailed chart review was conducted to obtain more detailed information regarding surgery and the bacterial origins of endocarditis.

The institutional ethics committee and review board of Asan Medical Center approved the present study (No. 2017-0657). The requirement for informed patient consent was waived due to the retrospective nature of the study.

2) Surgery and postoperative treatment

The indications for surgery were the presence of $>$10 mm of vegetation, local uncontrolled infection, and signs or symptoms of heart failure resulting from valve dehiscence or severe prosthetic valve dysfunction. All operations were performed with CPB, which was used with systemic normothermia or mild hypothermia (32^{o}C). Previously implanted prostheses were totally removed, and abscesses and fistulas were thoroughly debrided. The choice of the new prosthesis was made at the discretion of the surgeon. Concomitant procedures were performed if needed.

3) Statistical analysis

Categorical variables are expressed in frequencies and percentages, and continuous variables are presented as mean±standard deviation. The Kaplan-Meier method was used to delineate overall mortality, and differences in the survival rates were assessed by the log-rank test.

Cox proportional hazard models were performed to assess the effects of variables on the risk of overall mortality. First, potential risk factors were identified through the univariable analysis, and significant variables ($p<0.1$) were included in the multivariable Cox regression analysis with stepwise backward elimination. Results are expressed as hazard ratio (HRs) with 95% confidence intervals (CIs). A priori factors were emphasized in the process of selecting variables, and p-values <0.05 were considered to indicate statistical significance. All data were analyzed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA).

Results

1) Baseline patient characteristics and preoperative findings

Table 1 shows the clinical characteristics of the study group of 84 patients. Early PVE, which was defined as PVE diagnosed within 60 days of prosthetic valve implantation [7], was present in 9 cases (10.7%). In 54 cases (64.3%), PVE occurred in patients who had a mechanical valve, and the remaining 30 cases (35.7%) were in patients who had a bioprosthetic valve. Of the 30 patients with bioprosthetic valve endocarditis, 21 patients underwent urgent or emergency surgery, while 9 patients underwent delayed surgery after medical treatment failure. The indications for surgery in the former 21 patients who underwent emergency surgery were severe valve dysfunction in 9, abscess formation or infection caused by a multi-resistant organism in 8, and high embolic risks in 4. Among the total of 84 subjects, a prosthetic aortic valve was implanted in 60 patients (71.4%) and a prosthetic mitral valve in 45 patients (53.6%). Echocardiography revealed vegetation in 62 cases (73.8%) and an abscess in 62 (73.8%).

Table 1. Baseline characteristics of the patients

Characteristic	Value
No. of patients	84
Age (yr)	54.8±12.7
Sex (male)	51 (60.7)
Early PVE	9 (10.7)
Late PVE	75 (89.3)
Body mass index (kg/m^2)	22.4±3.3
Diabetes mellitus	7 (8.3)
Hypertension	19 (22.6)
Serum creatinine (mg/dL)	1.25±0.9
On hemodialysis	2 (2.4)
Current cerebrovascular accident	31 (36.9)
Left ventricle ejection fraction (%)	57.1±9.8
No. of previous operations	
1	63 (75.0)
2	17 (20.2)
3	3 (3.6)
4	1 (1.2)
Prior inserted valve	
Mechanical	54 (64.3)
Bioprosthetic	30 (35.7)
Single valve affected	61(72.6)
Aortic valve	38 (45.2)
Mitral valve	23 (27.4)
Multiple valves affected	23 (27.4)
Aortic+mitral	22 (26.2)
Mitral+tricuspid	1 (1.2)
Vegetation formation	62 (73.8)
Abscess formation	62 (73.8)

Values are presented as mean±standard deviation or number (%).
PVE, prosthetic valve endocarditis.

Table 2. Bacterial origins of endocarditis

Variable	Total (n=84)	Early PVE (n=9)	Late PVE (n=75)
Coagulase-negative Staphylococci	23 (27.4)	3 (33.3)	20 (26.7)
Staphylococcus aureus	20 (23.8)	4 (44.4)	16 (21.3)
Methicillin-susceptible	11 (13.1)	2 (22.2)	9 (12.0)
Methicillin-resistant	9 (10.7)	2 (22.2)	7 (9.3)
Viridans group Streptococci	7 (8.3)	-	7 (9.3)
Other Streptococci	6 (7.1)	-	6 (8.0)
Enterococci	3 (3.6)	-	3 (4.0)
Fungus	1 (1.2)	1 (11.1)	-
Others	3 (3.6)	-	3 (4.0)
Negative culture	21 (25)	1 (11.1)	20 (26.7)

Values are presented as number (%).
PVE, prosthetic valve endocarditis.

Table 3. Details of surgery

Variable	Value
Operative procedures	
AVR	21 (25.0)
MVR	18 (21.4)
AVR+MVR	21 (25.0)
Bentall procedure	18 (21.4)
Bentall procedure+MVR	4 (4.8)
Tricuspid valve replacement	2 (2.4)
Prosthetic valve type	
Mechanical valve	55 (65.5)
Tissue valve	23 (27.4)
Homograft	6 (7.1)
Associated procedures	
Mitral-aortic intervalvular fibrosa reconstruction	17 (20.2)
Coronary artery bypass grafting	4 (4.8)
Tricuspid annuloplasty	7 (8.3)
Cardiopulmonary bypass time (min)	279.1±123.3
Aortic cross-clamp time (min)	169.9±72.1

Values are presented as number (%) or mean±standard deviation.
AVR, aortic valve replacement; MVR, mitral valve replacement.

2) Microbiologic data

Table 2 summarizes the causative microbes of early and late PVE. Coagulase-negative Staphylococci were the most common causative organism, appearing in 23 cases (27.4%), and *Staphylococcus aureus* was the next most common, in 20 cases (23.8%). Viridans group Streptococci and other Streptococci were only found in the late PVE group (9.3% and 8.0%, respectively). Twenty-one cases (25%) returned culture-negative.

3) Surgical profiles

The patients' surgical profiles are summarized in Table 3. Mechanical valves, bioprostheses, and homografts were used to replace infected prostheses in 55 (65.5%), 23 (27.4%), and 6 patients (7.1%), respectively. Concomitant procedures included mitral-aortic intervalvular fibrosa reconstruction in 17 patients (20.2%), coronary artery bypass grafting in 4 (4.8%), and tricuspid annuloplasty in 7 (8.3%). The mean CPB and aortic cross-clamp (ACC) times were 279.1± 123.3 minutes and 169.9±72.1 minutes, respectively.

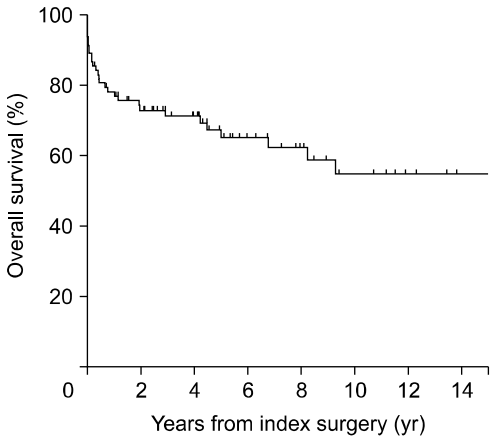
4) Operative outcomes

The early and late surgical outcomes are summar-

Table 4. Operative outcomes

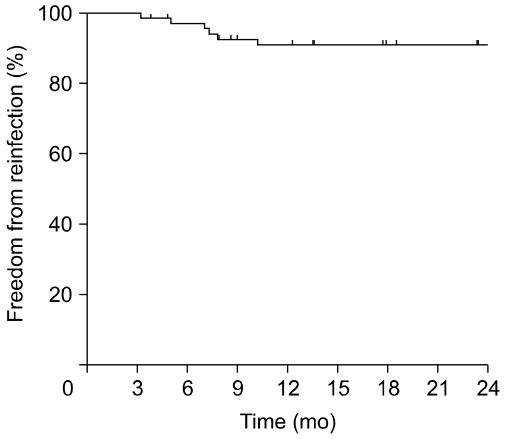
Variable	Value
Early adverse outcomes	
In-hospital death	10 (11.9)
Major complications	37 (44.0)
Continuous renal replacement therapy	17 (20.2)
Cerebrovascular accident	15 (17.9)
Surgical site bleeding	14 (16.7)
Extracorporeal membrane oxygenation insertion	10 (11.9)
Intra-aortic balloon pump	1 (1.2)
Respiratory complication	2 (2.4)
Late adverse outcomes	
Death	22 (5.0)[a]
Reinfection	6 (0.8)[a]
Reoperation	6 (0.8)[a]

Values are presented as number (%).
[a]Percentage per patient-year.



Time (yr)	0	2	4	6	8	10	12	14
No. of patient at risk	84	53	40	25	19	14	9	7
No. of events	0	23	1	3	1	2	0	0

Fig. 1. Kaplan-Meier curve for overall survival.



Time (yr)	0	3	6	9	12	15	18	21	24
No. of patient at risk	84	69	65	59	57	54	52	51	49
No. of events	0	1	1	3	1	0	0	0	0

Fig. 2. Kaplan-Meier curve for freedom from reinfection.

ized in Table 4. The perioperative complications included reoperation for bleeding in 14 patients (16.7%), renal failure requiring continuous renal replacement therapy in 17 (20.8%), cerebrovascular accident (CVA) events in 15 (17.9%) and low cardiac output syndrome requiring extracorporeal membrane oxygenation in 10 (11.9%).

The median follow-up duration was 47.3 months (range, 0 to 250 months). In-hospital death occurred in 10 patients (11.9%). The overall survival rates at 5 and 10 years were 64.4%±5.8% and 54.3%±7.3%, respectively (Fig. 1).

A recurrent episode of valve infection was detected in 6 cases (7.1%): 5 in mechanical valves and 1 in a bioprosthetic valve (Supplementary Table 1). All cases of reinfection occurred within the first year after surgery, and the mean time to reoperation after PVE surgery was 6.7±2.4 months. The freedom from reinfection rate at 5 years was 91.0%±3.5% (Fig. 2).

5) Risk factor analysis

Both univariable and multivariable analyses were performed with Cox proportional hazard models to identify the variables affecting overall survival. In the univariable analysis, factors associated with poor overall survival were older age, the presence of vegetation detected by echocardiography or during surgery, current CVA, longer CPB time, and longer ACC time. In the multivariable analysis, older age (HR, 1.48; 95% CI, 1.05 to 2.10; p=0.027) and longer CPB time (HR, 1.03; 95% CI, 1.00 to 1.01; p=0.033) were significantly associated with an increased risk for overall mortality (Table 5).

Discussion

As the frequency of valve replacement increases with progress in open heart surgery, PVE has become a serious problem. PVE is a severe, catastrophic complication, and results in valve dysfunc-

Table 5. Results of univariable and multivariable analyses: risk factors for overall death

Predictors of overall survival	Hazard ratio (95% confidence interval)	p-value
Cox univariable analysis		
Age	1.63 (1.16–2.29)	0.005
Current stroke	2.10 (1.02–4.33)	0.045
Vegetation	3.83 (1.17–12.6)	0.027
Cardiopulmonary bypass time	1.04 (1.02–1.07)	0.002
Aortic cross-clamp time	1.05 (1.00–1.10)	0.041
No. of previous operation	0.63 (0.30–1.30)	0.206
Bacteria	1.01 (0.90–1.13)	0.919
Mitral-aortic intervalvular fibrosa reconstruction	1.50 (0.67–3.35)	0.323
Cox multivariable analysis		
Age (/10 yr)	1.48 (1.05–2.10)	0.027
Cardiopulmonary bypass time (/10 min)	1.03 (1.00–1.01)	0.033

tion and paravalvular leakage, thereby leading to heart failure, embolism, and high morbidity and mortality.

In 1963, Geraci et al. [8] reported that endocarditis occurred in about 10% of patients who did not receive antibiotic prophylaxis prior to receiving prosthetic valve replacement; the authors termed this PVE, distinct from NVE. Conventionally, cases of infection in which clinical symptoms or signs are detected during the first 60 days after surgery have been referred to as "early PVE," and those detected later than 60 days as "late PVE" [9]. However, it has been suggested that rather than 60 days, the 1-year mark after operation should be used to discriminate between early PVE and late PVE due to the absence of a significant difference in the bacterial strains identified between 60 days and 1 year after operation [10]. Following this criterion, infection occurring between 60 days and 1 year could be additionally classified as "intermediate PVE" [11].

Previous studies have shown different causative organisms in early and late PVE. Early PVE is likely to be attributable to perioperative bacteremia or by contamination of the prosthetic valve at the time of implantation. Common sources of bacteremia include wound infections, urogenital infections, pneumonia, and intravascular catheter-related infections [12]. Coagulase-negative Staphylococci and *S. aureus* are the most frequently encountered pathogens, followed by Gram-negative bacilli and fungal infection in the setting of early PVE [13]. The causative pathogens for late PVE are similar to those of NVE such as Streptococci, *S. aureus*, coagulase-negative Staphylococci, and Enterococci, which are more likely to be associated with skin infections, oral and gastrointestinal infections, and invasive orodental procedures [12,14]. For these reasons, the current practice guidelines recommend that patients with prosthetic valves should be administered appropriate broad-spectrum antibiotics when undergoing procedures that can lead to significant bacteremia, such as orodental, gastrointestinal, and urogenital procedures [15]. In the present study, coagulase-negative Staphylococci were the most common organisms present in cases of late PVE (26.7%, 20 of 75), while *S. aureus* prevailed in early PVE (44.4%, 4 of 9); these observations are compatible with the findings of prior studies. Streptococcal infection was only confirmed in the late PVE group.

Many studies have reported that *S. aureus* in PVE is associated with a poor prognosis [6,16,17], and the presence of *S. aureus* has been suggested to be an indication for early surgery [15]. However, we did not find a clear association between the causative microorganisms and clinical outcomes.

Postoperative complications, including bleeding, respiratory complications, low cardiac output, and renal dysfunction, occur intermittently [12]. In this study, postoperative complications were observed in approximately 40% of patients. Previous studies have found neurologic complications to be associated with adverse outcomes [17], but our data did not clearly show such a relationship.

Recent reports have shown that the in-hospital mortality rate after surgery for PVE has fallen to approximately 13% [18,19], and our study showed a

similar but slightly lower in-hospital mortality rate of 11.9%. In 1998, Edwards et al. [20] reported that the overall survival at 5 years was 55% and the overall survival at 10 years was of 37.6% in 322 PVE patients. In 2012, Manne et al. [18] reported a 5-year survival rate of 63% in 180 PVE patients and in 2013, Edlin et al. [19] reported a 5-year survival rate of 65% in 56 PVE patients. Similarly to those studies, our study showed overall survival rates of 64.4% and 50.4% at 5 and 10 years after surgery, respectively, indicating that the long-term mortality after PVE surgery was also quite high. In other words, in-hospital mortality and the late outcomes of surgical treatment of PVE have yet to be significantly improved.

Predictors of in-hospital mortality have been reported to include increased age [20,21], female sex, longer bypass time during the operation [22], abscess [23], emergency surgery, poor hemodynamic status [24], staphylococcal infection [16], renal dysfunction [25], and multiple previous operations [26]. Several reports have analyzed the predictors of late outcomes after surgery for PVE. Previously, it has been repeatedly reported that older age adversely affects long-term survival after PVE surgery [27]; additionally, poor left ventricular function, the complexity of the procedure [28], and double valve surgery have been reported to be possible predictors of poor long-term survival [29]. In this study, the number of in-hospital deaths was too small to find statistical significance for the related factors. The multivariable analysis showed that older age and longer CPB time were associated with poor overall survival. CPB time has been identified as an independent risk factor for poor outcomes of cardiac surgery in a number of published series; however, it also may be a surrogate marker of complexity and the challenging nature of the higher-risk surgical procedures in this particular subset of patients.

Reinfection and reoperation after surgery are also important surgical outcomes. Musci et al. [30] reported that these events occurred within the first year after operation. Freedom from reoperation at 10 years due to reinfection after surgery for early and late PVE was reported to be 85.8% and 92.1%, respectively. In 2014, Grubitzsch et al. [29] reported that freedom from reoperation due to reinfection was 91.3% at 10 years. Comparably, a total of 6 reinfection events (7.1%) occurred in this study, all within the first year after PVE surgery. The freedom from reinfection rate was 91.0% at 5 years.

This study has several limitations. First, since PVE is a rare complication, the statistical significance of possible predictors was not completely reliable due to the small number of patients. Additionally, because the current study was retrospective, observational, and nonrandomized, it may have been prone to selection bias or information bias. In addition, because the results of this study were from a single center (a tertiary-care teaching hospital), there is a possibility of referral bias.

In conclusion, PVE is a severe complication after cardiac valve replacement, and it has been reported to pose a high risk of in-hospital mortality as well as poor long-term survival. This retrospective study showed that older age and longer CPB time were associated with an increased risk of overall mortality. Additional studies are needed to establish therapeutic strategies for this potentially fatal complication.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.5090/kjtcs.2018.51.1.15. Supplementary Table 1. Details of reinfection.

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