Surgical Results of Third or More Cardiac Valve Operation

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Background: We evaluated operative outcomes after third or more cardiac operations for valvular heart disease, and analyzed whether pericardial coverage with artificial membrane is helpful for subsequent reoperation. ***Methods:*** From 2000 to 2012, 149 patients (male : female=70 : 79; mean age at operation, 57.0±11.3 years) underwent their third to fifth operations for valvular heart disease. Early results were compared between patients who underwent their third operation (n=114) and those who underwent fourth or fifth operation (n=35). Outcomes were also compared between 71 patients who had their pericardium open during the previous operation and 27 patients who had artificial membrane coverage. ***Results:*** Intraoperative adverse events occurred in 22 patients (14.8%). Right atrium (n=6) and innominate vein (n=5) were most frequently injured. In-hospital mortality rate was 9.4%. Total cardiopulmonary bypass time (225±77 minutes vs. 287±134 minutes, p=0.012) and the time required to prepare aortic cross clamp (209±57 minutes vs. 259±68 minutes, p＜0.001) increased as reoperations were repeated. However, intraoperative event rate (13.2% vs. 20.0%), in-hospital mortality (9.6% vs. 8.6%) and postoperative complications were not statistically different according to the number of previous operations. Pericardial closure using artificial membrane at previous operation was not beneficial in reducing intraoperative events (25.9% vs. 18.3%) and shortening operation time preparing aortic cross clamp (248±64 minutes vs. 225±59 minutes) as compared to no-closure. ***Conclusion:*** Clinical outcomes of the third or more operations for valvular heart disease were acceptable in terms of intraoperative adverse events and in-hospital mortality rates. There were no differences in the incidence of intraoperative adverse events, early mortality and postoperative complications between third cardiac operation and fourth or more.

Key words: 1. Reoperation
2. Sternum
3. Pericardium
4. Outcomes
5. Valve disease

INTRODUCTION

Operations requiring resternotomy account for approximately 10% of all cardiac operations, and this proportion might increase in the future [1]. Although the risk involved in a patient's second cardiac surgery has decreased [2,3], reported morbidity and mortality rates after the third or subsequent cardiac operation are still high [4]. In addition, previous studies have demonstrated that injury during sternal re-entry or intrapericardial dissection is related to operative

Table 1. Preoperative characteristics and comorbidities of the study patients

Variable	Total (n=149)	3rd operation (n=114)	4th or 5th operation (n=35)	p-value
Age (yr)	57.0±11.3	56.7±11.1	58.0±12.0	0.539
Male : female	79 : 70	64 : 50	15 : 20	0.168
Risk factors				
Smoking	10 (6.7)	7 (6.1)	3 (8.6)	0.700
Diabetes mellitus	12 (8.1)	9 (7.9)	3 (8.6)	>0.999
Hypertension	30 (20.1)	20 (17.5)	10 (28.6)	0.155
History of stroke	23 (15.4)	17 (14.9)	6 (17.1)	0.749
Chronic kidney disease	5 (3.4)	3 (2.6)	2 (5.7)	0.335
Infective endocarditis	15 (10.1)	10 (8.8)	5 (14.3)	0.343
Connective tissue disease	6 (4.1)	4 (3.5)	2 (5.7)	0.626
New York Heart Association class ≥3	79 (53.0)	61 (53.5)	18 (51.4)	0.829
Ejection fraction (%)	56.2±10.1	55.5±10.5	58.6±8.6	0.109
Duration from last operation (mo)	130.7±70.1	142.5±64.5	92.4±74.7	<0.001

Values are presented as mean±standard deviation or number (%).

Table 2. Primary cause of reoperation

Variable	Total (n=149)	3rd operation (n=114)	4th or 5th operation (n=35)	p-value
Prosthetic valve failure	115 (77.2)	80 (70.2)	35 (100.0)	<0.001
Paravalvular leakage of prosthetic mitral valve	76 (51.0)	49 (43.0)	27 (77.1)	<0.001
Paravalvular leakage of prosthetic aortic valve	13 (8.7)	8 (7.0)	5 (14.3)	0.183
Stenosis of prosthetic aortic valve	9 (6.0)	9 (7.9)	0	0.117
Stenosis of prosthetic mitral valve	4 (2.7)	4 (3.5)	0	0.573
Stenosis of prosthetic tricuspid valve	3 (2.0)	3 (2.6)	0	>0.999
Infective endocarditis	10 (6.7)	7 (6.1)	3 (8.6)	0.700
Progression of native valve disease	34 (22.8)	34 (29.8)	0	<0.001
Tricuspid regurgitation	28 (18.8)	28 (24.6)	0	<0.001
Aortic regurgitation	3 (2.0)	3 (2.6)	0	>0.999
Aortic stenosis	2 (1.3)	2 (1.8)	0	>0.999
Mitral regurgitation	1 (0.7)	1 (0.9)	0	>0.999

Values are presented as number (%).

mortality and morbidity [1]. The aims of this study were to evaluate operative outcomes in patients who underwent their third or subsequent cardiac operation for valvular heart disease, and to analyze whether pericardial coverage with an artificial membrane during the previous cardiac surgery improved outcomes.

METHODS

1) Patient characteristics

Our study enrolled 149 patients (70 males and 79 females) who underwent their third to fifth cardiac operation for valvular heart disease from January 2000 to December 2012. It was the third cardiac operation for 114 patients, the fourth for 30 patients, and the fifth for five patients. Patients who had undergone previous operations for isolated coronary artery disease and aortic disease were excluded. We retrospectively reviewed all medical records and operation notes including both paper charts and electronic records. The mean age at operation was 57.0±11.3 years. Hypertension (n=30, 20.1%) and stroke (n=23, 15.4%) were common comorbidities (Table 1). The most common cause for reoperation was paravalvular leakage of a prosthetic mitral valve (n=73, 49.0%) (Table 2).

Table 3. Operative data of the study patients

Variable	Total (n=149)	3rd operation (n=114)	4th or 5th operation (n=35)	p-value
Operation data				
CPB time (min)	240±97	225±77	287±134	0.012
ACC time (min)	130±60	125±52	144±80	0.109
Preparation for ACC (min)[a]	231±61	209±57	259±68	<0.001
Type of operation				
Single valve operation	99 (66.4)	73 (64.0)	26 (74.3)	0.261
Mitral valve	50 (33.6)	30 (26.3)	20 (57.1)	0.001
Aortic valve	20 (13.4)	14 (12.3)	6 (17.1)	0.460
Tricuspid valve	29 (19.5)	29 (25.4)	0	<0.001
Double valve operation	47 (31.5)	38 (33.3)	9 (25.7)	0.396
Mitral+aortic valve	11 (7.4)	7 (6.1)	4 (11.4)	0.287
Mitral+tricuspid valve	23 (15.4)	18 (15.8)	5 (14.3)	0.829
Aortic+tricuspid valve	13 (8.7)	13 (11.4)	0	0.039
Triple valve operation	3 (2.6)	3 (2.6)	0	>0.999
Arrhythmia surgery	6 (4.0)	6 (5.3)	0	0.336
Coronary artery bypass graft	3 (2.0)	3 (2.6)	0	>0.999
Aortic surgery	13 (8.7)	10 (8.8)	3 (8.6)	>0.999
Planned CPB before sternotomy	18 (12.1)	14 (12.3)	4 (11.4)	>0.999
Via femoral artery	17 (11.4)	13 (11.4)	4 (11.4)	>0.999
Via axillary artery	1 (0.7)	1 (0.9)	0	>0.999

Values are presented as mean±standard deviation or number (%).
CPB, cardiopulmonary bypass; ACC, aortic cross clamp.
[a]The time spent from skin incision to starting aortic cross clamp.

2) Operative strategy

Preoperative computed tomography evaluation was performed on all patients. Patients were laid on the operation table after an external defibrillating paddle was placed on their backs. After untwisting and lifting the previous sternal wires, the sternum was divided using reciprocating and oscillating saws. In 18 patients, cardiopulmonary bypass (CPB) through the femoral (n=17) or axillary (n=1) artery was initiated before sternal re-entry at the discretion of the operating surgeon in order to prevent cardiac injury. In addition, 10 patients needed an emergency femoro-femoral bypass due to injury during retrosternal (n=7) or intrapericardial (n=3) dissection. During previous operations, the cardiac chambers of 51 patients had been covered with native pericardium and the cardiac chambers of 27 patients had been covered with a Gore Preclude expanded polytetrafluoroethylene (ePTFE) pericardial membrane (W. L. Gore and Associates Inc., Flagstaff, AZ, USA). The remaining 71 patients had no pericardial coverage from previous operations. After careful intrapericardial dis-

section, CPB was administered with routine aorto-bicaval cannulation. All operations were performed under moderate hypothermia and cold intermittent cardioplegic arrest. Mitral, aortic, and tricuspid valve surgery was performed in 87, 46, and 72 patients, respectively. Concomitant procedures included aortic surgery (n=13) and coronary artery bypass grafting (n=3) (Table 3). At the end of the operation, the pericardium was fully closed if there was enough native pericardium to cover it. Otherwise, it was either left open or closed with an artificial membrane at the discretion of the operating surgeon. However, the ascending aorta was always covered with native tissue, such as the thymic fat pad, even when the pericardium was left open.

3) Evaluation of clinical outcomes

Early mortality was defined as death before release from the hospital or within 30 days after surgery. We considered the following adverse intraoperative events: (1) injury to any of the four cardiac chambers; (2) injury to major vessels such as the aorta, vena cavae, arch vessels, and coronary artery;

and (3) critical arrhythmias such as ventricular tachycardia and ventricular fibrillation [5]. Early post-surgical outcomes were compared between patients who underwent their third cardiac operation (n=114) and those who underwent their fourth or fifth operation (n=35). Clinical outcomes were also compared between patients whose pericardium was left open during a previous operation (n=71) and those who had artificial membranes put in place (n=27), in order to analyze the effectiveness of pericardial coverage using an artificial membrane. Patients in whom the pericardium was only covered around the ascending aorta or along less than the upper one-third of the anterior surface of the heart were considered to have an open pericardium. Morbidities were defined as follows. Low cardiac output syndrome was defined as a cardiac index <2.0 L/min/m^2 or a systolic arterial pressure <90 mmHg, requiring an intra-aortic balloon pump insertion or inotropic support using dopamine or dobutamine in quantities >5 mg/kg/min. A postoperative cerebrovascular event was defined as a diagnosis of a new focal neurologic deficit, confirmed by a neurologist using an appropriate brain imaging technique such as computed tomography or magnetic resonance imaging. Acute kidney injury was defined as an increase in the serum creatinine level of 50% or more compared to the preoperative value or as the need for renal replacement therapy. Pneumonia was recorded if a clinical diagnosis was made with symptoms, imaging, and microbiological confirmation.

4) Statistical analysis

Statistical analyses were performed using the PASW SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis was performed using the chi-squared test or Fisher's exact test for categorical variables, and Student t-test for continuous variables. Multivariable analysis was performed for outcome variables that were statistically significant or nearly significant in univariate analysis; multiple linear regression was used for continuous variables and logistic regression was used for categorical variables. All preoperative and intraoperative factors, including categorical and continuous variables, were subjected to univariate analysis, and variables with a p-value <0.10 in univariate analysis were entered into the multivariable analysis. p-values <0.05 were considered statistically significant.

RESULTS

1) Clinical outcomes

Twenty-four adverse intraoperative events occurred in 22 patients (14.8%). The right atrium was the most frequently injured structure (n=6), followed by the innominate vein (n=5), right ventricle (n=4), and aorta (n=3). There was one occurrence of ventricular fibrillation during sternal re-entry (Table 4). The adverse event rate was not significantly different between the third operation and fourth or fifth operations (13.2% [15 of 114 patients] vs. 20.0% [7 of 35 patients], p=0.318). Early mortality occurred in 9.4% of patients (14 of 149). The rate of early mortality was 9.6% among patients undergoing their third operation, compared to 8.6% among patients undergoing their fourth or fifth operation (p=0.848). Postoperative complications included low cardiac output syndrome (n=42, 28.2%), stroke (n=8, 5.4%), and acute kidney injury (n=12, 8.1%). There was no significant difference in the rate of either early mortality or postoperative complications according to the number of the operation (Table 5).

2) Usefulness of pericardial coverage using an expanded polytetrafluoroethylene membrane

Clinical outcomes were compared between patients in whom the pericardium was closed with an ePTFE membrane in a previous operation (n=27) and those in whom the peri-

Table 4. Types of intraoperative adverse events in 22 patients

Intraoperative adverse event	No.
Cardiac injuries	
Right atrium	6
Innominate vein	5
Right ventricle	4
Aorta	3
Superior vena cava	1
Inferior vena cava	1
Innominate artery	1
Right coronary artery	1
Right pulmonary artery	1
Ventricular fibrillation	1
Total	24

Table 5. Comparison of intraoperative adverse event, early mortality, and morbidities between third and fourth or more cardiac operation

Variable	3rd operation (n=114)	4th or 5th operation (n=35)	p-value
Intraoperative adverse event	15 (13.2)	7 (20.0)	0.318
Emergency cardiopulmonary bypass due to adverse event	7 (6.1)	3 (8.6)	0.700
Early mortality	11 (9.6)	3 (8.6)	0.848
Morbidity			
Low cardiac output syndrome	32 (28.1)	10 (28.6)	0.954
Postoperative cerebrovascular accident	8 (7.0)	0	0.107
Acute kidney injury	10 (8.8)	2 (5.7)	0.561
Reoperation for bleeding	11 (9.6)	2 (5.7)	0.471
Pneumonia	34 (29.8)	5 (14.3)	0.067

Values are presented as number (%).

cardium was left open (n=71). The only significant differences between these groups regarding preoperative risk factors were history of stroke (p=0.002) and infective endocarditis (p=0.012). No significant differences were found between the two groups regarding the incidence of intraoperative adverse events, early mortality, or postoperative complications. In addition, the preparation time for the aortic cross-clamp was longer in the group of patients whose pericardium had been previously closed, with a marginal level of significance (248±64 minutes vs. 225±59 minutes; p=0.090; β ±standard error= 23.396±13.680) (Table 6). However, multivariable linear regression showed that this difference was statistically insignificant, after adjusting for other factors such as age, sex, and number of previous sternotomies (p=0.150, β ±standard error= 6.289±13.023) (Table 7).

DISCUSSION

This study demonstrated three main findings. The clinical outcomes of patients' third or subsequent operations for valvular heart disease were acceptable in terms of adverse intraoperative events and in-hospital mortality rates. There was no difference between the third cardiac operation and the fourth or fifth cardiac operation with regard to early outcomes, including the incidence of intraoperative adverse events, early mortality, and postoperative complications. The preventive strategy of covering the pericardium with an artificial membrane may not be necessary in order to improve clinical outcomes in subsequent reoperations.

Many studies reported that multiple reoperations are a risk

factor for cardiac injury. The reported incidence of cardiac injury during the third or subsequent cardiac operation ranges from 14.0% to 15.1%, and the early mortality rate ranges from 8.9% to 9.0% [1,6]. These ranges are in agreement with the present results, in which the incidence of adverse events and early mortality rate are 14.8% and 9.4%, respectively. However, in contrast to previous studies, our study revealed that the results of the fourth or fifth cardiac surgery were comparable to those of the third cardiac surgery in terms of cardiac injury, in-hospital mortality, and postoperative morbidities, although the number of subjects enrolled was relatively small.

Previous studies have reported that CPB support was used in 2.6% to 79.8% of patients during sternal re-entry [7,8]. In the present study, CPB was used in 28 patients (18.8%) during sternal re-entry or mediastinal dissection. Ten of these patients (6.7%) needed emergency CPB support due to adverse intraoperative events. A previous study has evaluated the results of routine application of CPB before sternal re-entry, suggesting that extracorporeal circulation before a resternotomy can reduce the risk of major vascular structure injury, provide easy and reliable repair if injuries occur, and shorten overall operative time [9]. However, we did not routinely apply CPB before sternal re-entry due to concerns about prolonged CPB time, the harmful effects of retrograde perfusion such as aortic dissection and embolic stroke, and access site complications such as vascular injury, wound infection, and distal malperfusion.

There is no doubt that if the native pericardium is large enough, it should be closed at the end of the operation.

Table 6. Comparison between membrane closure and no closure groups

Variable	Membrane closure (n=27)	No closure (n=71)	p-value
Age (yr)	56.4±11.6	57.5±11.3	0.667
Male : female	17 : 10	35 : 36	0.226
Risk factors			
Smoking	2 (7.4)	3 (4.2)	0.614
Diabetes mellitus	0	8 (11.3)	0.102
Hypertension	8 (29.6)	14 (19.7)	0.293
History of stroke	9 (33.3)	6 (8.5)	0.002
Chronic kidney disease	1 (3.7)	1 (1.4)	0.477
Infective endocarditis	6 (22.2)	3 (4.2)	0.012
Connective tissue disease	3 (11.1)	2 (2.8)	0.127
New York Heart Association class ≥3	10 (37.0)	40 (56.3)	0.088
Type of operation			
Single valve operation	23 (85.2)	47 (66.2)	0.063
Double valve operation	4 (14.8)	12 (32.4)	0.128
Triple valve operation	0	1 (1.4)	>0.999
Operation data			
CPB time (min)	267±137	234±91	0.164
ACC time (min)	143±83	118±53	0.083
Preparation for ACC (min)[a]	248±64	225±59	0.090
Adverse event	7 (25.9)	13 (18.3)	0.403
During sternotomy	3 (11.1)	7 (9.9)	>0.999
During intrapericardial dissection	4 (14.8)	6 (8.5)	0.456
CPB strategy			
Routine CPB during sternal reentry	1 (3.7)	11 (15.5)	0.170
Emergent CPB due to adverse event	3 (11.1)	7 (9.9)	>0.999
Early mortality	4 (14.8)	6 (8.5)	0.456
Morbidity			
Low cardiac output syndrome	10 (37.0)	21 (29.6)	0.478
Postoperative cerebrovascular accident	1 (3.7)	3 (4.2)	>0.999
Acute kidney injury	4 (14.8)	2 (2.8)	0.047
Bleeding	3 (11.1)	5 (7.0)	0.681
Pneumonia	8 (29.6)	21 (29.6)	0.996

Values are presented as mean±standard deviation or number (%).
CPB, cardiopulmonary bypass; ACC, aortic cross clamp.
[a]The time spent from skin incision to starting aortic cross clamp.

Table 7. Multivariable linear regression analysis to identify factors associated with preparation time for aortic cross clamp time in patients with no pericardial closure or artificial membrane closure during previous operation

Variable[a]	Univariate		Multivariable	
	β ±standard error	p-value	β ±standard error	p-value
Artificial membrane closure	23.396±13.680	0.090	6.289±13.023	0.630
Age (yr)	1.009±0.539	0.064	0.672±0.496	0.179
Sex (reference=female)	−23.195±12.253	0.061	−25.912±11.365	0.025
No. of previous operation	44.795±10.396	<0.001	44.174±10.705	<0.001

[a]All preoperative and intraoperative factors from were analyzed and only variables that entered into multivariable analysis were demonstrated.

When performing cardiac valve surgery on a patient for the first time, the pericardium can be easily closed in most patients. However, during subsequent operations, the residual pericardium is often too small to cover the anterior surface of the heart, as shown by the fact that only one-third of the patients in the present study had undergone native pericardial closure during their previous operations. Surgeons in favor of pericardial closure argue that it has several advantages. First, closing the pericardium can minimize postoperative adhesions and provide sufficient retrosternal distance, which improves patient safety during repeated sternotomies [10,11]. In addition, recompartmentalization of the intrapericardial microenvironment and the mediastinum may be facilitated by closing the pericardium, which separates the heart from extrapericardial blood and other substances, such as cytokines and proinflammatory mediators, that cause postoperative adhesions and post-pericardiotomy syndrome [12,13]. Finally, some insist that cardiac hemodynamics can be improved by pericardial closure because the intact pericardium is able to modulate coupling between the left and right ventricles [14]. The ePTFE membrane is the most widely utilized synthetic surgical membrane for pericardial closure when native pericardium is unavailable. Previous studies have shown that it has non-adhesive qualities and allows resternotomies to be performed [15,16]. Despite these favorable reports, the routine application of ePTFE for pericardial closure has been called into question because some potentially crucial disadvantages have been identified. Both human [17] and animal [18] studies have demonstrated that ePTFE may aggravate the normal epicardial reaction, resulting in the deposition of a thick, fibrous, and often hemorrhagic layer that obscures the epicardial anatomy, interfering with safe sternal re-entry and dissection of the intrapericardial space. In the present study, we found that closing the pericardium with ePTFE did not improve the incidence of adverse events compared to leaving the pericardium open. In addition, the artificial membrane made the dissection of cardiac structures to apply the aortic cross-clamp more time-consuming, although the difference was not statistically significant. This corroborated previous findings indicating that ePTFE membranes can interfere with the epicardial anatomy [17,18].

The present study has some limitations. First, this is a ret-rospective, observational study conducted at a single institution. Second, the number of study patients, especially the number of patients who underwent a fourth or fifth operation, was too small to allow a definite conclusion to be drawn.

CONFLICT OF INTEREST

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

ACKNOWLEDGMENTS

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