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Myocardial Injury Following Aortic Valve Replacement for Severe Aortic Stenosis: Risk Factor of Postoperative Myocardial Injury and Its Impact on Long-Term Outcomes

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Background: As hypertrophied myocardium predisposes the patient to decreased tolerance to ischemia and increased reperfusion injury, myocardial protection is of utmost importance in patients undergoing aortic valve replacement (AVR) for severe aortic valve stenosis (AS). ***Methods:*** Consecutive 314 patients (mean age, 62.5±10.8 years; 143 females) with severe AS undergoing isolated AVR were included. Postoperative myocardial injury (PMI) was defined as 1) maximum postoperative creatinine kinase isoenzyme MB or troponin-I levels ≥10 times of reference, 2) postoperative low cardiac output syndrome or episodes of ventricular arrhythmia, or 3) left ventricular ejection fraction of less than 55% and decrease in left ventricle (LV) ejection fraction of more than 20% of the baseline value. ***Results:*** There were 90 patients (28.7%) who developed PMI. There were five cases of early death (1.6%), all of whom had PMI. On multivariable analysis, the use of histidine-tryptophan-ketoglutarate (HTK) solution instead of blood cardioplegia (odds ratio [OR], 3.06; 95% confidence interval [CI], 1.63 to 5.77; p=0.001), greater LV mass (OR, 1.04; 95% CI, 1.01 to 1.07; p=0.007), and increased cardiac ischemic time (OR, 1.13; 95% CI, 1.05 to 1.22; p<0.001) were independent predictors for PMI. Patients who had PMI showed significantly inferior long-term survival than those without PMI (p=0.049). ***Conclusion:*** PMI occurred in a considerable proportion of patients undergoing AVR for severe AS and was associated with poor long-term survival. HTK cardioplegia, higher LV mass, and longer cardiac ischemic duration were suggested as predictors of myocardial injury.

Key words: 1. Myocardial injury
2. Aortic valve
3. Surgery

INTRODUCTION

Aortic valve stenosis (AS) is the most common valvular disease in the western countries, and approximately 4% of people older than 65 years are reported to have severe AS [1]. For instance, approximately 50,000 cases of AVR for severe AS are being performed annually in the United States, and these are predicted to increase by one and a half times by the year 2030 [2]. Severe AS can predispose the patient to symptoms of chest pain, syncope, and dyspnea, and the prognosis is reported to be very disappointing when these symptoms accompany. The average survival rate of these patients has been reported as only two years, and the five-year survival rate has been reported to be only 12% to 20% if the con-

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dition is not treated surgically [3,4]. Surgical aortic valve replacement (AVR) is a well-proven standard treatment of severe AS, and it has shown normalization of survival in selected populations [5].

Despite progresses in myocardial protection strategies, cardiopulmonary bypass (CPB), surgical techniques, and perioperative management, the mortality and morbidity rates following AVR for severe AS are still not negligible with the reported mortality rates being 2.6% to 4.0% [2,6]. The left ventricular (LV) wall is usually hypertrophied as the consequence of pressure overloading due to valvular obstruction, which develops gradually over several decades. Accordingly, delivery of a cardioplegic solution may be suboptimal in the hypertrophied LV wall, particularly in the endocardial area. Therefore, myocardial protection of AVR for AS still remains challenging, and hence, significant postoperative myocardial injury (PMI) after AVR for severe AS is the leading cause of early death [7].

In order to improve myocardial protection during AVR for AS, a number of studies have been conducted including those seeking ideal routes of cardioplegic solution delivery or types of cardioplegic solution, and those determining factors related to PMI [8-15]. These studies, however, are limited by experimental study designs and have shown mixed results. Therefore, there are only few comprehensive clinical studies that assess the risk factors for PMI in the setting of isolated AVR for AS with a reasonably sized cohort. Therefore, we sought to evaluate the incidence of PMI in patients undergoing isolated AVR for severe AS, and to determine the risk factors of PMI.

METHODS

1) Study population

Between August 1999 and July 2009, a total of 340 patients underwent elective isolated AVR for severe AS at the Asan Medical Center, Seoul, Korea. Patients were excluded if they had significant (>grade 2) aortic regurgitation (n=16) or significant (>grade 2) mitral regurgitation (n=9) because these factors can affect the analyses as confounding variables. Finally, 314 patients formed the subject population of this study. The requirement to obtain informed consent was waived by the institutional review board due to the retrospective nature of the study.

2) Surgical techniques

Surgery involved a median sternotomy (n=304) or a limited sternotomy including upper sternotomy (n=8) or transverse sternotomy (n=2), depending on the preference of the surgeon. The sternotomy approach involved conventional bicaval (n=170) or single venous (n=134) combined with distal ascending aorta cannulation, whereas limited sternotomy (n=10) involved femoral and internal jugular venous cannulation. For myocardial protection, tepid blood cardioplegia (n=253) or histidine-tryptophan-ketoglutarate (HTK-Custodiol; Koehler Chemi, Alsbach-Haenlien, Germany) solution (n=61) was administered after aortic clamping under CPB, depending on the preference of the surgeon. Routes of cardioplegic delivery were 'antegrade' via aortic root cannula or directly through coronary ostia in 175 patients (n=175), 'retrograde' via coronary sinus in 16 patients (blood cardioplegia in 13 patients, HTK solution in 3 patients), or combined antegrade and retrograde in 123 patients (blood cardioplegia in 104 patients, HTK solution in 19 patients).

3) Postoperative monitoring and measurement of cardiac marker proteins

All patients were transferred to the intensive care unit after the operation, and hemodynamic monitoring was carried out by the measurement of arterial pressure, central venous pressure, and pulmonary artery pressure, continuously. Cardiac enzyme levels including those of creatinine kinase isoenzyme MB (CK-MB) and troponin-I were measured immediately after surgery and at postoperative 6, 12, and 24 hours. If any cardiac enzyme increased until 24 hours after the operation, additional measurements of the cardiac enzymes were carried out. The upper normal reference value of CK-MB and troponin I were defined as 'less than 5 ng/mL' and 'less than 1.5 ng/mL,' respectively.

4) Definition of perioperative significant myocardial injury and follow-up

Significant perioperative myocardial injury was defined if any of the following criteria were satisfied [11,12,15,16]: (1)

Table 1. Baseline characteristics of patients

Variable	Myocardial injury (+)	Myocardial injury (-)	p-value
No.of patients	90 (28.7)	224 (71.3)	
Female gender	33 (36.7)	110 (49.1)	0.06
Age (yr)	63.1±9.5	62.2±11.4	0.54
Body surface area (m^2)	1.67±0.17	1.63±0.17	0.08
Diabetes mellitus	15 (16.7)	31 (13.8)	0.522
Hypertension	38 (42.2)	75 (68.2)	0.145
Preoperative echocardiography			
LVID in systole (mm)	34.0±9.2	30.4±8.0	0.02*
LVID in diastole (mm)	51.3±8.1	47.9±6.4	0.01*
LV ejection fraction (%)	57.2±12.5	59.6±11.2	0.12
LV mass (g)	308.9±107.9	267.3±83.8	<0.001*
LV mass index (g/m^2)	183.2±65.6	164.1±50.0	0.014*
Aortic valve area (cm^2)	0.60±0.18	0.60±0.16	0.989
Peak trans-aortic PG (mmHg)	108.7±28.7	101.0±28.1	0.03*
Mean trans-aortic PG (mmHg)	67.2±18.7	63.5±18.4	0.12

Values are presented as number (%) or mean±standard deviation.
LVID, left ventricular internal dimension; LV, left ventricle; PG, pressure gradient.
*p-value < 0.05.

peak venous blood CK-MB or troponin-I levels of above 10 times the reference values; (2) postoperative low cardiac output syndrome (LCOS), which is defined as the documented low cardiac index (< 2.0) despite adequate volume including the needs for mechanical circulatory support including intra-aortic balloon pump, extracorporeal membrane oxygenator (ECMO), and ventricular assisting device; (3) any episodes of ventricular tachycardia or fibrillation during the postoperative hospitalization period; and (4) LV dysfunction, which is defined as an LV ejection fraction (LVEF) of less than 55% and a decrease in LVEF of more than 20% of the baseline value on early postoperative echocardiography. Clinical follow-up was performed via outpatient clinic visits. For the patients who underwent follow-up at outside hospitals, clinical information was obtained by telephone contact. All deaths were regarded as cardiac origin unless a non-cardiac origin was diagnosed clinically or was determined at autopsy.

5) Statistical analysis

Categorical variables are expressed as frequencies and percentages. Chi-square test or Fisher's exact test were used to compare. Continuous variables are presented as a mean with standard deviation or a median with ranges. Student's unpaired t-test was used to compare. Kaplan- Meier curves were used to delineate the overall survival. Univariable and multivariable risk factor analyses were performed by using the multiple logistic regression method. Variables with a p-value of 0.20 or less in the univariable analyses were candidates for the multivariable models. Multivariable analyses involved a backward elimination technique, and variables with a p-value of less than 0.10 remained in the final model. All reported p-values were two-sided, and a value of $p < 0.05$ was considered statistically significant. For the statistical analysis, PASW SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

1) Baseline patient profiles

The baseline characteristics of the patients are listed in Tables 1, 2. Patients who were affected by PMI had larger LV dimension, greater LV mass/LV mass index, and greater peak trans-aortic pressure gradient than those without PMI. The HTK crystalloid cardioplegia was more frequently used in patients with PMI, and the routes for cardioplegic delivery were significantly different between the two groups of patients (Table 2).

Table 2. Baseline characteristics of the patients (operative factor)

Variable	Myocardial injury (+)	Myocardial injury (-)	p-value
Cardiopulmonary bypass time (min)	135.9±61.5	106.4±37.6	<0.001*
Aortic cross-clamping time (min)	86.6±44.4	70.1±26.6	<0.001*
Cardioplegic solution type			0.004*
Blood cardioplegia	63 (70.0)	190 (84.8)	
Histidine-tryptophan-ketoglutarate solution	27 (30.0)	34 (15.2)	
Cardioplegic solution infusion route			0.036*
Antegrade	40 (44.4)	135 (60.3)	
Retrograde	5 (5.6)	11 (4.9)	
Combined	45 (50.0)	78 (34.8)	
Lowest esophageal temperature (°C)	29.6±2.6	29.8±2.6	0.568
Concomitant aortic replacement	8 (8.9)	11 (4.9)	0.181

Values are presented as mean±standard deviation or number (%).
*p-value < 0.05.

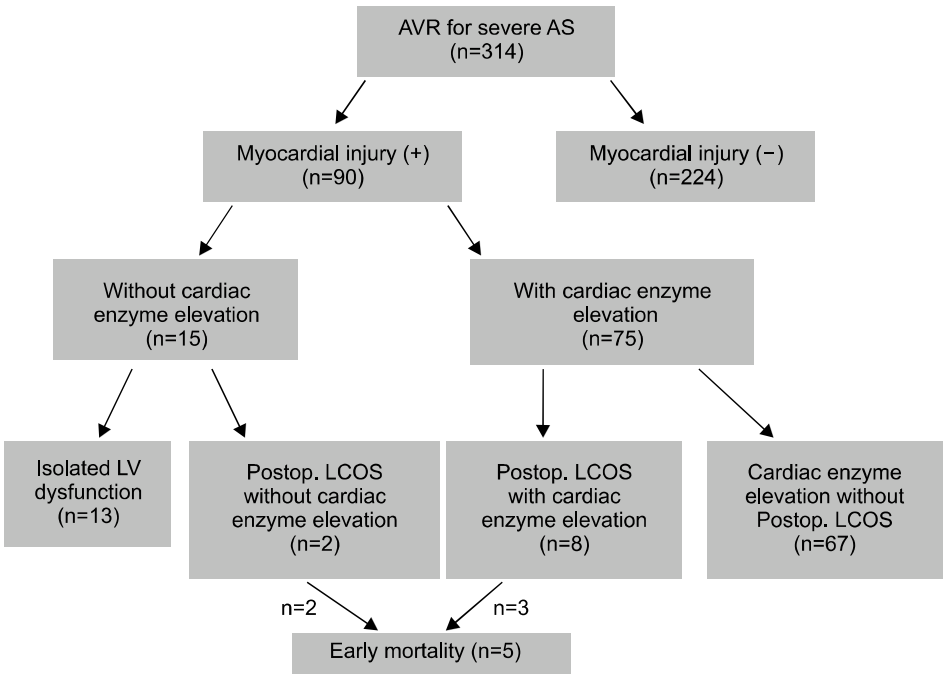

Fig. 1. Relationship between significant myocardial injury and early clinical outcomes. AVR, aortic valve replacement; AS, aortic valve stenosis; LV, left ventricle; Postop, postoperative; LCOS, low cardiac output syndrome.

2) Myocardial injury and early outcomes

The relationship between myocardial injury and early clinical outcomes is shown in Fig. 1. There were 90 patients (28.7%) who developed significant myocardial injury. Of these patients, 67 had isolated cardiac enzyme elevation, 10 had LCOS with (n=8) or without (n=2) cardiac enzyme elevation, and 13 had isolated LV dysfunction on echocardiography (Fig. 1).

There were five early deaths (1.6%), all of whom had myocardial injury and received HTK cardioplegia during AVR. Of them, three patients required ECMO support postoperatively and died on ECMO. Another patient died of infective endocarditis that occurred at the implanted bioprosthetic aortic valve followed by septic shock. The other patient died of recurrent ventricular fibrillation that was refractory to electrical defibrillation. The patient was one of four ventricular arrhythmia events that occurred during

Table 3. Multivariable analysis for risk factors of postoperative myocardial injury

Variable	Hazard ratio	95% confidence interval	p-value
Use of histidine-tryptophan-ketoglutarate solution	3.06	1.63-5.77	0.001
Left ventricular mass, by 1 g increment	1.04	1.01-1.07	0.007
Aortic clamping time, by 1 min increment	1.13	1.05-1.22	<0.001
Cardiopulmonary bypass time, by 1 min increment	1.12	1.06-1.19	<0.001

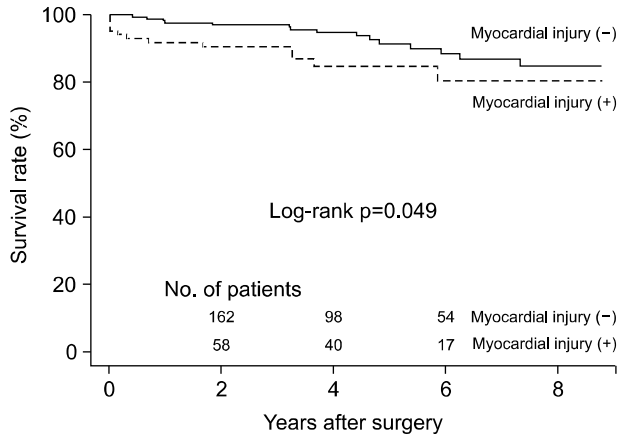

Fig. 2. Kaplan-Meier curves for the overall survival rate.

hospitalization. On multivariable analysis, the use of the HTK solution instead of blood cardioplegics, higher LV mass, and longer aortic clamping and CPB times emerged as significant and independent risk factors of PMI (Table 3).

3) Late outcomes

Clinical follow-up was complete in all patients with a mean follow-up duration of 47.5±33.7 months (median, 42.3 months; range, 0.23 to 120.4 months). During follow-up, there were 23 late cardiac-related deaths (overall 26 late deaths), 8 in the myocardial injury group and 15 in the non-myocardial injury group. The Kaplan-Meier curves for the overall survival of the two groups are shown in Fig. 2. The 5-year survival rates were 85.0%±4.3% and 91.5%±2.6% in the patients with and without PMI, respectively (p=0.049).

DISCUSSION

In the present study, we found that PMI occurred in a considerable proportion of patients undergoing surgical AVR for severe AS, and the overall survival was significantly affected by the occurrence of PMI. Independent determinants of PMI were longer cardiac ischemic time, greater LV mass, and the use of HTK solution instead of blood cardioplegia.

There have been several studies on the use of HTK solution for myocardial protection in cardiac surgery [15,17]. These studies have shown that the use of HTK solution is as safe as that of tepid blood cardioplegia with excellent early outcomes. Taking a more detailed look at these data, the present study was conducted in the setting of a mitral valve operation. The LV in the presence of severe AS is commonly hypertrophied, and therefore, the vulnerability of the myocardium against ischemia differs from that of the LV affected by the mitral valvular disease. In one study, a significantly higher rate of spontaneous ventricular fibrillation after cross-clamp removal in patients receiving HTK was observed than in those receiving blood cardioplegia [15]. Another prospective randomized study in the setting of coronary artery bypass grafting (CABG) reported that there were no significant differences in the incidence of PMI, rate of early complications, and clinical outcomes depending on the use of 'blood cardioplegia' versus 'crystalloid cardioplegia' [11]. In contrast to our study population, the cited study was performed on patients who underwent CABG. Therefore, the nature of cardioplegic delivery through the coronary vasculature might be different from that in our study population, which can explain our study result. Moreover, the mean aortic clamping time of the cited study was only 34 minutes, and this is very little time to evaluate the effect of myocardial protection. Meanwhile, a meta-analysis was performed including randomized clinical trials that compared blood cardioplegia and crystalloid cardioplegia in heterogeneous cardiac operations [12]. In the meta-analysis, blood cardioplegia provided significantly superior myocardial protection in terms of low incidence of the postoperative LCOS and low levels of cardiac markers. The results of the meta-analysis are comparable to those of

the present study. Braathen and Tonnessen [13] performed a prospective randomized study to determine the optimal type of cardioplegia for myocardial protection in the setting of isolated AVR for isolated AS. In the cited study, the maximum blood levels of cardiac marker proteins including CK-MB and troponin-T were higher with the use of 'crystalloid cardioplegia' over 'blood cardioplegia.' This corresponds well with the results of our present study. The cited study, however, did not compare long-term outcomes between the two groups and did not use the HTK solution as the crystalloid cardioplegia. In the literature review, we could not identify a study that compared the cardio-protective effect between the HTK solution and tepid blood cardioplegia in the setting of isolated AVR for severe AS. Therefore, the results of our study need to be verified by further studies with prospective designs.

Longer cardiac ischemic times during a cardiac operation have been well established as potent risk factors associated with poor early and long-term outcomes by numerous previous studies. Prolonged cardiac ischemic times can cause ischemic complications in various organs including the central nervous system, gastrointestinal tract, kidney, and coronary artery system [18-20]. In our study, longer cardiac ischemic times were an independent risk factor for PMI on the multivariable analysis, and the results are well correlated with those of previous studies. Accordingly, the results of our study provide further support for the importance of minimizing the ischemic time. Therefore, as is well known, efforts for minimizing the myocardial ischemic time should be made during cardiac operations.

The myocardial protective effect of cardioplegia can be also influenced by the administration route [10]. In the present study, antegrade cardioplegia was more frequently used in patients who were not affected by PMI. Nevertheless, the route of cardioplegia administration was not revealed as an independent risk factor for PMI on the multivariable analysis. Although we tried to control the potential confounding effects of other variables such as LV dimension, LV mass, CPB time, and the type of cardioplegia in the multivariable analysis, the confounding effects of these variables might not have been fully controlled during the analysis due to the limited number of patients. In the same context, numerous studies have been performed to identify the optimal method of blood cardioplegia regarding the infusion rate (continuous vs. intermittent) and the temperature of blood cardioplegia (cold vs. warm). Although there are many studies regarding these issues, the optimal method of blood cardioplegia is still under debate due to the diverse results of these studies. Therefore, the effects of the infusion route and the infusion methods of cardioplegia necessitate further studies in the future involving a fairly homogenous population, preferably in prospective randomized settings. Categorizing patients into six subgroups based on the administration routes (antegrade, retrograde, and combined) and the types (HTK vs. blood) of cardioplegia may be ideal for fair comparisons to evaluate the effects of the mode of cardioplegic administration. Nevertheless, these analyses were impossible in this study because only 3 patients received HTK cardioplegia via a retrograde route and 9 patients received HTK cardioplegia via a combined antero- and retrograde route. This asymmetry in the number of patients in each category hindered adequate statistical comparisons among the different groups; therefore, this factor might have become a confounder in the statistical analysis even though we considered it to be one of the covariates in the multivariable models.

This study is subject to the limitations inherent in retrospective work with observational data. The non-randomized design may have affected the results due to unmeasured confounders, procedures, or detection bias. Another limitation is the insufficient data of preoperative echocardiography, which can influence clinical outcomes.

In conclusion, myocardial injury occurred in a considerable proportion of patients undergoing AVR for severe AS and was associated with poor long-term survival. The use of HTK solution for myocardial protection, greater LV mass, and longer cardiac ischemic duration were suggested as predictors of myocardial injury. The study results need to be verified by further prospective studies involving larger populations.

CONFLICT OF INTEREST

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

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