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Clinical Results of Different Myocardial Protection Techniques in Aortic Stenosis

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Background: Hypertrophied myocardium is especially vulnerable to ischemic injury. This study aimed to compare the early and late clinical outcomes of three different methods of myocardial protection in patients with aortic stenosis. ***Methods:*** This retrospective study included 225 consecutive patients (mean age, 65±10 years; 123 males) with severe aortic stenosis who underwent aortic valve replacement. Patients were excluded if they had coronary artery disease, an ejection fraction ＜50%, more than mild aortic regurgitation, or endocarditis. The patients were divided into three groups: group A, which was treated with antegrade and retrograde cold blood cardioplegia; group B, which was treated with antegrade crystalloid cardioplegia using histidine-tryptophan-ketoglutarate (HTK) solution; and group C, treated with retrograde cold blood cardioplegia. ***Results:*** Group A contained 70 patients (31.1%), group B contained 74 patients (32.9%), and group C contained 81 patients (36%). The three groups showed significant differences with regard to the proportion of patients with a New York Heart Association functional classification ≥III (p=0.035), N-terminal pro-brain natriuretic peptide levels (p=0.042), ejection fraction (p=0.035), left ventricular dimensions (p＜0.001), left ventricular mass index (p＜0.001), and right ventricular systolic pressure (p ＜0.001). Differences in cardiopulmonary bypass time (p=0.532) and aortic cross-clamp time (p=0.48) among the three groups were not statistically significant. During postoperative recovery, no significant differences were found regarding the use of inotropes (p=0.328), mechanical support (n=0), arrhythmias (atrial fibrillation, p=0.347; non-sustained ventricular tachycardia, p=0.1), and ventilator support time (p=0.162). No operative mortality occurred. Similarly, no significant differences were found in long-term outcomes. ***Conclusion:*** Although the three groups showed some significant differences with regard to patient characteristics, both antegrade crystalloid cardioplegia with HTK solution and retrograde cold blood cardioplegia led to early and late clinical results similar to those achieved with combined antegrade and retrograde cold blood cardioplegia.

Key words: 1. Aortic valve
2. Replacement
3. Myocardial reperfusion injury
4. Cardioplegic solutions
5. Retrograde

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INTRODUCTION

Protecting the myocardium during ischemic cardiac arrest is essential for successful surgical outcomes. Despite extensive experimental and clinical research, it has not been possible to define an optimal method of myocardial protection due to the diverse pathophysiology of diseases whose surgical treatment involves ischemic cardiac arrest and the wide range of surgical situations that may occur. Moreover, most the current literature consists of studies that were conducted to evaluate treatment strategies for coronary artery disease [1]. The results from such studies cannot be directly applied to the treatment of aortic stenosis, because aortic stenosis and coronary artery disease are associated with different metabolic dynamics [2].

In aortic valve surgery, the antegrade delivery of cardioplegic solution via the aortic root is generally accepted. However, when aortic regurgitation (AR) occurs, the antegrade method may not be effective. Rapid venting of the left ventricle through a vent catheter or squeezing of the left ventricle during the delivery of cardioplegic solution can be an effective option. Direct coronary ostial cannulation is also possible, but it may result in late coronary ostial stenosis [3]. Retrograde coronary sinus perfusion of cardioplegic solution may be a promising technique in the presence of significant AR; however, concerns about the efficacy and the safety of this technique with regard to the protection of the right ventricle and the posterior ventricular septum have limited its use [4].

Previous experimental and clinical studies have shown conflicting results regarding the outcome of retrograde coronary sinus blood cardioplegia. Several studies in the early 1990s suggested that retrograde coronary sinus blood cardioplegia may provide optimal myocardial protection [5]. However, the myocardial protection provided retrograde blood cardioplegia was proven to be inferior to that provided by antegrade blood cardioplegia, based on the assessment of biochemical markers and metabolic responses [5,6]. The complexity of these results was mostly due to the small numbers of patients studied as well as the heterogeneous techniques and operative procedures employed in these studies [7,8]. Moreover, previous studies have not demonstrated any differences in clinical outcome when antegrade blood cardioplegia is compared to retrograde cardioplegia or antegrade crystalloid cardioplegia [5-8]. This study aimed to compare the clinical efficacy of these three different methods of myocardial protection in the treatment of aortic stenosis. In order to minimize potentially confounding variables, we only included aortic stenosis patients without coronary artery disease, and all patients were operated on and managed by a single surgeon.

METHODS

1) Patients

This retrospective study included 225 consecutive patients who underwent aortic valve replacement performed by a single surgeon from January 1, 2000 to January 1, 2011 in the department of thoracic and cardiovascular surgery at our institution. Patients with severe aortic stenosis were included as the subjects. Patients were excluded if they had coronary artery stenosis ($>50\%$ stenosis in one or more major coronary artery as demonstrated by coronary angiography), an ejection fraction $<50\%$, moderate or severe AR, endocarditis, or a history of previous cardiac surgery. Since 2000, our institution's standard protocol for myocardial protection in aortic valve replacement procedures has been either combined antegrade and retrograde cold blood cardioplegia or antegrade crystalloid cardioplegia. In patients with severe aortic stenosis accompanied by mild AR, we prefer retrograde cold blood cardioplegia alone, since direct coronary ostial infusion of the cardioplegic solution may result in early myocardial infarction and late coronary ostial stenosis that causes myocardial ischemia [3]. The subjects were divided into three groups. Group A was treated with antegrade and retrograde cold blood cardioplegia, group B was treated with antegrade crystalloid cardioplegia using histidine-tryptophan-ketoglutarate (HTK) solution, and group C was treated with retrograde cold blood cardioplegia. The clinical records, operation records, and laboratory records of each patient were reviewed. Our institutional review board approved the study protocol and waived the need for consent from patients or relatives due to the retrospective nature of the study.

2) Operative techniques

Consistent anesthetic and operative techniques were used throughout the study period. After median sternotomy, car-

diopulmonary bypass (CPB) was established between the ascending aorta and the two individually cannulated venae cavae, which were snared shortly after the onset of bypass. Full systemic heparinization was applied, with an activated clotting time >480 seconds. The circuits were primed with 200 mL of albumin, 500 mL of pentastarch, 50 mL/kg of mannitol, 300 mL of plasma solution, 60 mEq of sodium bicarbonate, 500 mg of methylprednisolone, 1 g of $MgSO_4$, 1 g of tranexamic acid, and 300,000 U of ulinastatin. Mild hypothermia was instituted immediately after CPB was initiated. Ventricular fibrillation was then induced with a fibrillator as soon as the ascending aorta was cross-clamped. A left ventricular vent line was immediately introduced via the right upper pulmonary vein. During the operation, the cardiac index was kept at 2.4 L/m^2 during normothermia, and lowered to 2.0 to 2.4 L/m^2 during hypothermia. Spaghetti or pledgeted 2-0 polyester sutures were placed in a horizontal mattress fashion in the aortic annulus in order to provide a seat for the supra-annular placement of the prosthesis. The types of prostheses were determined by the preference of the surgeon. Conventional and modified ultrafiltration were used in all operations. The patients were rewarmed to 36°C before CPB was terminated.

3) Myocardial protection

If minimal or no AR was present, combined antegrade and retrograde cold blood cardioplegia or antegrade crystalloid cardioplegia using HTK solution was preferred. In patients with mild AR as shown by preoperative echocardiography, retrograde cold cardioplegia was preferred. In all groups, moderate hypothermia (range, 28°C to 32°C) was applied.

(1) Group A: antegrade and retrograde cold blood cardioplegia: As soon as the ascending aorta was cross-clamped, electromechanical quiescence was rapidly established using a fibrillator in conjunction with the administration of cold blood cardioplegia into the aortic root. Through a small right atriotomy, a balloon-tipped catheter (a 14-Fr Foley catheter) was placed under direct vision into the terminal portion of the coronary sinus after placing a purse-string suture around the coronary sinus ostium. A coronary sinus ostial occlusion was made by tightening the purse-string suture and the balloon was gently inflated to approximately 1 to 2 mL. The catheter was then withdrawn and was nested on the purse-string closure. Retrograde maintenance cold blood cardioplegia was then delivered every 20 to 25 minutes or at every occurrence of electromechanical activity. The cardioplegic solution was infused at 4°C. The induction cardioplegic solution was a 4:1 mixture of Joongwae cardioplegic solution 1 (JW Pharmaceutical, Seoul, Korea) and blood, combined with 80 mEq/L of K^+ and 20 mEq/L of sodium bicarbonate. Maintenance cardioplegia was accomplished using a 4:1 mixture of Joongwae cardioplegic solution 1 (JW Pharmaceutical) and blood combined with 20 mEq/L of K^+ and 20 mEq/L of sodium bicarbonate.

(2) Group B: antegrade crystalloid cardioplegia using HTK solution: As with group A, in group B, antegrade cardioplegic solution was administered through the aortic root shortly after aortic cross-clamping. Rapid electromechanical quiescence was established by a fibrillator in conjunction with the delivery of cardioplegic solution. There was a single delivery of 2 L of HTK solution (Custodiol; Koehler Chemi, Alsbach-Haenlien, Germany) at a temperature of 5°C to 8°C.

(3) Group C: retrograde cold blood cardioplegia: After CPB was established, both caval cannulas were snared. A short right atriotomy was performed on the beating heart, and retrograde cardioplegia delivery was performed as described above. As soon as the ascending aorta was cross-clamped, the fibrillator was operated in conjunction with retrograde delivery of cold blood cardioplegia. An aortotomy was then performed to confirm that the cardioplegic solution was draining into the coronary ostia. Maintenance cardioplegic solution was then delivered every 20 to 25 minutes, or whenever there was any evidence of electromechanical activity. The solutions used were identical to those used in group A. Coronary sinus pressure was not measured routinely.

4) Definitions and follow-up

Operative mortality was defined as any postoperative death occurring within 30 days or during the same hospital admission. Low cardiac output syndrome was diagnosed if the patient required an intra-aortic balloon pump in order to be weaned from CPB due to hemodynamic compromise, either in the operating theater or in the intensive care unit. Low cardiac output syndrome was also diagnosed if the pa-

tient required inotropic medication (dopamine, dobutamine, milirone, or epinephrine) in order to maintain a systolic blood pressure of 90 mmHg and/or a cardiac output of 2.2 L/min/m^2 for 30 minutes in the intensive care unit, after electrolyte and blood gas abnormalities were corrected and after the preload was adjusted to its optimal value. Patients who received less than 4 mcg/kg/min of dopamine or a sub-therapeutic dose of dobutamine (2 mcg/kg/min) were not considered to have low cardiac output syndrome. Postoperative arrhythmia was diagnosed in cases of sustained new-onset supraventricular tachyarrhythmia necessitating antiarrhythmic therapy, regardless of whether direct current cardioversion was needed, in cases of ventricular tachycardia or fibrillation, regardless of whether direct current shock was needed, and in cases of sustained conduction defects. Clinical follow-up was carried out via outpatient clinic visits. Clinical information regarding patients who underwent follow-up at outside hospitals was obtained by telephone.

5) Statistical analysis

Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or the Fisher's exact test. Continuous variables were presented as mean±standard deviation and compared using unidirectional analysis of variance. Kaplan-Meier curves were used to express overall survival rates. All p-values < 0.05 were considered to indicate statistical significance. IBM SPSS ver. 22.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis.

RESULTS

1) Preoperative characteristics of the patients

The preoperative characteristics of the patients are shown in Table 1. Patients in group C showed significantly higher N-terminal pro-brain natriuretic peptide levels, higher EuroSCOREs, slightly lower ejection fraction values, larger left ventricular dimensions, and greater left ventricular mass index values. This is consistent with the fact that most of the patients in group C had mild AR (n=64, 79%). Three patients with previous myocardial infarctions (more than three months prior) were included in group B, but they were proven not to have significant coronary artery disease at the time of operation. Otherwise, there were no significant differences between the three groups with regard to preoperative characteristics.

2) Intraoperative data and early outcomes

The intraoperative data showed no significant differences in CPB time (p=0.523) or aortic cross-clamp time (p=0.48) among the three groups (Table 2). Moreover, no significant differences were observed in post-arrest recovery time (p=0.408), as calculated by subtracting the aortic cross-clamp time from the CPB time (Table 2). These findings may partially be due to the fact that we used a fibrillator along with administering cardioplegic solution in order to induce rapid electromechanical quiescence, but we have no direct empirical support.

No statistically significant differences were seen in early postoperative variables (Table 3). No patients needed mechanical circulatory support after the operation. No differences among the three groups were found in the use of inotropics (p=0.328) or the incidence of arrhythmias (atrial fibrillation, p=0.347; non-sustained ventricular tachycardia, p=0.1). There were no instances of operative mortality.

3) Late outcomes

Clinical follow-up was completed in all patients, with a mean follow-up duration of 70.71±36 months (median, 61.75 months; range, 2 to 163 months). During the follow-up period, 15 late deaths occurred (Table 4). Six deaths were due to malignancies and three deaths were due to unknown causes. There were six late cardiac-related deaths: three in group A, two in group B, and one in group C. There were no statistically significant differences in the occurrence of late cardiac-related death (p=0.510). If deaths from unknown causes are regarded as cardiac-related deaths, then five late cardiac-related deaths occurred in group A, two in group B, and two in group C (p=0.27). Kaplan-Meier curves expressing the overall survival rates and freedom from cardiac-related mortality in each group are shown in Fig. 1 and Fig. 2.

DISCUSSION

It is well known that hypertrophied myocardium is more

Table 1. Preoperative characteristics of the patients

Variable	Group A (n=70, 31.1%)	Group B (n=74, 32.9%)	Group C (n=81, 36%)	p-value
Age (yr)	61.94±10.41	66.21±9.65	67.5±9.42	0.002*
Male patients	42 (60.0)	35 (47.3)	36 (56.8)	0.276
Body surface area (m^2)	1.69±0.18	1.65±0.17	1.64±0.18	0.327
Diabetes mellitus	14 (20.0)	11 (14.9)	17 (21.0)	0.585
Hypertension	31 (44.3)	31 (41.9)	37 (45.7)	0.892
Cerebrovascular accidents	2 (3.0)	3 (4.0)	6 (7.0)	0.399
Chronic lung disease	2 (2.9)	4 (5.0)	5 (2.2)	0.062
Chronic kidney disease	2 (3.0)	0	0	0.107
Carotid artery disease	9 (18.0)	14 (22.2)	30 (45.5)	0.002*
Previous myocardial infarction	0	3 (4.1)	0	0.045*
New York Heart Association functional classes III and IV	16 (40.0)	7 (20.0)	20 (20.0)	0.035*
N-terminal pro-brain natriuretic peptide levels (pg/mL)	813.5±12	725.09±12	1,210.38±1,309.87	0.042*
Preoperative inotropics use	0	1 (1.4)	0	0.359
Preoperative ventilator use	0	0	1 (1.2)	0.409
EuroSCORE	4.2±1.81	4.97±1.88	5.02±2.07	0.017*
Logistic EuroSCORE	3.35±2.6	4.16±2.52	4.56±4.57	0.093
Atrial fibrillation	7 (10.0)	7 (9.5)	3 (3.7)	0.259
Preoperative echocardiography				
Preoperative aortic regurgitation				
None	13 (18.6)	33 (44.6)	4 (4.9)	0.000
Minimal	28 (40.0)	39 (52.7)	13 (16.0)	
Mild	29 (41.40)	2 (2.7)	64 (79.0)	
Mean transaortic pressure gradient (mmHg)	56.91±15.07	62.95±23.45	62.86±16.92	0.089
Peak aortic jet velocity (m/sec)	4.89±0.65	5±0.81	5.05±0.63	0.366
Aortic valve area (cm^2)	0.69±0.15	0.7±0.19	0.7±0.17	0.866
Ejection fraction (%)	64.17±6.95	65.55±6.22	62.89±5.87	0.035*
LVID in diastole (mm)	50.64±5.35	49.26±4.69	52.41±5.68	0.001*
LVID in systole (mm)	30.23±4.47	28.81±4.1	31.9±4.7	0*
Left ventricle mass index (g/m^2)	132.82±32.14	124.24±33.14	152.14±36.83	0*
Right ventricle systolic pressure gradient (mmHg)	39.33±11.14	31.8±7.69	35.53±8.97	0*
E/E'[a)]	14.3±5.47	14.46±6.58	15.6±9.04	0.535

Values are presented as mean±standard deviation or number (%).
LVID, left ventricular internal dimension.
[a)]The ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity. *p-value＜0.05.

vulnerable to ischemic injury [9]. Hypertrophied myocardium presents with dilated epicardial coronary arteries, along with reduced capillary density and vascular dilatation reserve in the subendocardial region [10]. After reperfusion, the myocardium is even more vulnerable to ischemic injury due to the rapid loss of high-energy phosphate, the increased accumulation of lactate and H+, the premature occurrence of ischemic contracture, and accelerated calcium overload [2,11,12]. The above factors may also lead to hypotension and ventricular fibrillation, which can easily develop into subendocardial ischemia and necrosis. Techniques for myocardial protection have mostly been developed and investigated in the clinical setting of coronary bypass surgery [1]. The choice of the optimal myocardial protection technique in patients with hypertrophied myocardium remains controversial [13]. Furthermore, the metabolic differences between hearts with ischemic disease and hypertrophic hearts with aortic valve disease mean that the traditional cardioplegic techniques that were de-

Table 2. Intraoperative data

Variable	Group A (n=70, 31.1%)	Group B (n=74, 32.9%)	Group C (n=81, 36%)	p-value
Combined operation				
Maze operation	5 (7.1)	5 (6.8)	3 (3.7)	0.064
Ascending aorta wrapping	19 (27.1)	22 (29.7)	17 (21.0)	0.44
Ascending aorta replacement	3 (4.3)	4 (5.4)	4 (4.9)	0.952
Aortic root widening	3 (4.30)	2 (2.7)	1 (1.2)	0.51
Aortic root reconstruction	4 (5.7)	5 (6.8)	7 (8.6)	0.776
Myomectomy	8 (11.4)	21 (28.4)	7 (8.6)	0.002*
Mitral valve repair	4 (5.7)	3 (4.1)	5 (6.2)	0.83
Tricuspid valve repair	0	1 (1.4)	5 (6.2)	0.044*
Cardiopulmonary bypass time (min)	113±40.27	140.27±338.09	105.83±30.84	0.523
Aortic cross-clamp time (min)	84.94±28.56	85.65±64.52	78.05±25.83	0.48
Post-arrest recovery time (min)	56.80±276.23	25.79±13.90	36.50±158.86	0.408

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

Table 3. Early postoperative outcomes

Variable	Group A (n=70, 31.1%)	Group B (n=74, 32.9%)	Group C (n=81, 36%)	p-value
Ventilator support (hr)	13.36±8.96	27.86±102.11	10.88±4.45	0.162
Intensive care unit stay (day)	1.72±1.05	2.1±4.27	1.66±1.06	0.525
Hospital stay (day)	10.4±4.48	11.51±9.35	10.33±7.4	0.549
Low cardiac output syndrome				
Postoperative inotropics use	23 (32.9)	19 (25.7)	18 (22.2)	0.328
Intra-aortic balloon pump or extracorporeal membrane oxygenation	0	0	0	
Significant postoperative arrhythmia				
Atrial fibrillation	6 (8.6)	3 (4.1)	3 (3.7)	0.347
Non-sustained ventricular tachycardia	13 (18.6)	5 (6.8)	10 (12.3)	0.1
Paravalvular leak (early)	1 (1.4)	1 (1.4)	0	0.566
Postoperative bleeding				
Infective endocarditis	1 (1.4)	1 (1.4)	1 (1.2)	0.995
Patient prosthesis mismatch	0	0	1 (1.2)	0.409
Stroke	1 (1.4)	0	2 (2.5)	0.407
Infarction				
Hemorrhage	0	0	1 (1.2)	0.409
Mediastinitis	0	1 (1.4)	0	0.359
Operative mortality	0	0	0	

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

veloped for the management of ischemic heart disease may not be suitable for treating patients with hypertrophied myocardium [2].

Some possible techniques for myocardial protection in the treatment of aortic stenosis might include the use of crystalloid cardioplegia with HTK solution and the use of retrograde cold blood cardioplegia alone. HTK solution is attractive for cardiac surgeons because it is administered with a single dose and is claimed to offer myocardial protection for a period of up to three hours [13], allowing complex procedures to be performed without interruption. However, several previous studies have indicated that blood cardioplegia yields superior results, as shown by the lower release of cardiac biomarkers after declamping and better metabolic responses

Table 4. Late clinical outcomes

Variable	Total (n=225)	Group A (n=70, 31.1%)	Group B (n=74, 32.9%)	Group C (n=81, 36%)	p-value
Late morbidity					
Paravalvular leak	0	0	0	0	
Infective endocarditis	1 (0.4)	0	0	1 (1.2)	0.409
Pannus	1 (0.4)	1 (1.4)	0	0	0.329
Hemorrhage	1 (0.4)	0	0	1 (1.2)	0.409
Thrombosis	6 (2.7)	3 (4.3)	1 (1.4)	2 (2.5)	0.545
Patient prosthesis mismatch	4 (1.8)	2 (2.9)	1 (1.4)	1 (1.2)	0.711
Late mortality					
Cardiac-related	6 (2.7)	3 (4.3)	2 (2.7)	1 (1.2)	0.51
Unknown	3 (1.3)	2 (2.9)	0	1 (1.2)	0.326
Malignancy	6 (2.7)	2 (2.9)	0	4 (2.4)	0.161

Values are presented as number (%).

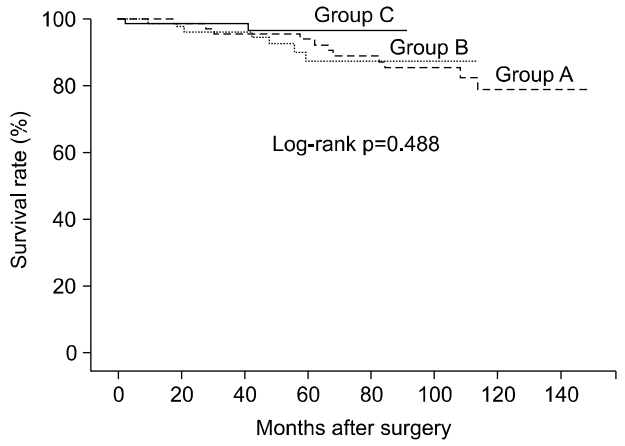

Fig. 1. Kaplan-Meier curves for the overall survival rate.

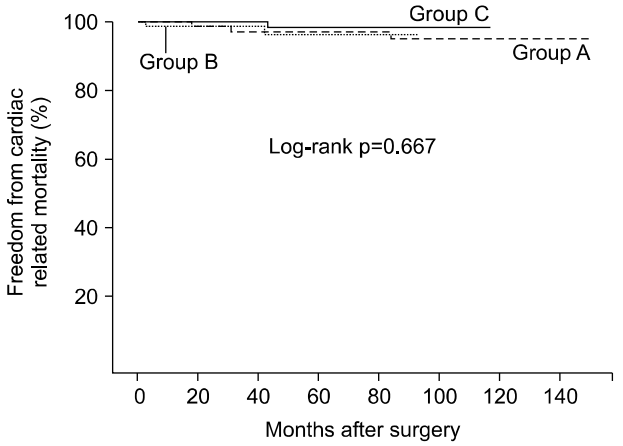

Fig. 2. Kaplan-Meier curves for freedom from cardiac related mortality.

[6,7,14,15]. However, these findings have not so far been confirmed by clinical outcomes. It is difficult to draw reliable conclusions about this issue due to the use of heterogeneous operative procedures, of which the most relevant factors are the wide range of pump times and the variable duration of cardiac arrest [8,16]. A prospective study comparing blood cardioplegia with crystalloid cardioplegia in patients with isolated aortic stenosis conducted by Ovrum et al. [13] found no difference in the clinical course of the patients. In their study, no statistically significant differences were seen regarding spontaneous sinus rhythm recovery after aortic declamping, the use of inotropic drugs, the duration of ventilator support, the occurrence of perioperative myocardial infarctions, episodes of atrial fibrillation, and mortality. A recent systematic review by Edelman et al. [17] is in agreement with these findings. This review included fourteen studies comparing crystalloid cardioplegia using HTK solution to conventional cardioplegia. Although the majority of studies included assessed the outcomes of coronary bypass graft surgery, no significant difference in mortality rates was found. Ventricular fibrillation was observed to have a higher incidence in the group treated with crystalloid cardioplegia using HTK solution, but this trend did not reach the level of statistical significance.

When AR is associated with aortic stenosis, the antegrade

delivery of cardioplegic solution may not be effective. Rapid venting of the left ventricle through a vent catheter or squeezing the left ventricle while cardioplegic solution is delivered can be a solution to this problem. Direct coronary ostial cannulation is another option, but it may result in coronary ostial stenosis [3]. Retrograde coronary sinus delivery of cardioplegic solution has been proposed to be a promising technique in the setting of significant AR [4]. The rationale for this is that retrograde delivery provides a relatively uniform distribution of cardioplegia. However, many anomalies and variations have been identified in the venous anatomy of the heart, and anatomic variations might affect the perfusion of the right ventricular free wall and septum during retrograde delivery [4]. Therefore, concerns about the efficacy and the safety of this procedure regarding the protection of the right ventricle and the posterior ventricular septum have limited its use [4]. Moreover, limited data exist regarding the use of retrograde blood cardioplegia alone in the treatment of aortic stenosis [1,7].

In the present study, we compared three different methods of myocardial protection in the treatment of aortic stenosis. Over time, the strategies used for myocardial protection in patients with aortic stenosis have changed at our institution. The method of combined antegrade and retrograde cold blood cardioplegia was initially applied in all cases. After accumulating sufficient experience and data, we found that there was little difference in post-arrest recovery and early outcomes when antegrade crystalloid cardioplegia with HTK solution or retrograde blood cardioplegia alone were used. Subsequently, our strategy has changed, such that antegrade crystalloid cardioplegia with HTK solution is used in cases of isolated aortic stenosis with insignificant AR and when the expected aortic cross-clamp time is less than two hours. Retrograde blood cardioplegia alone is now used when aortic stenosis is accompanied by significant AR.

During the cannulation of the coronary sinus for retrograde cardioplegia, we used a direct coronary sinus cannulation technique [18] with a 14-Fr Foley urinary catheter under an on-pump beating heart with bicaval cannulation. Although several techniques have been developed for the transatrial cannulation of the coronary sinus, they are nonetheless technically demanding procedures. Direct coronary sinus cannulation with a Foley urinary catheter under right atriotomy has the following advantages: (1) the closure with temporary sutures of large venous collaterals from the right atrial wall; (2) allowing the identification of small or underdeveloped coronary sinus orifices, which are very rare but require a quick conversion to antegrade perfusion; (3) preventing the leakage of retrograde cardioplegia through the coronary vein near the orifice of the coronary sinus; and (4) cost-effectiveness. After aortic cross-clamping, we apply a ventricular fibrillator to induce prompt cardiac arrest, regardless of the method of myocardial protection. Since it reduces the risk of an aortic tear during ventricular ejection after aortic cross-clamping [19], induced ventricular fibrillation may play an important role in our protocol, particularly when retrograde blood cardioplegia alone is used, because this method requires a longer time for inducing diastolic arrest. However, no published research has studied the efficacy of inducing ventricular fibrillation during aortic cross-clamping, so it is uncertain whether this technique may have affected the results of our study.

In the present study, we found no statistical difference in CPB weaning time among the three groups of patients, and no mechanical circulatory support was required. These results imply that the process of weaning was similar in all groups and suggest that the degree of myocardial damage after early reperfusion was similar, at least from a clinical perspective. Due to the retrospective design of the present study, no data were collected regarding cardiac rhythm during the CPB weaning process, the release of cardiac markers, and intraoperative measurements of ventricular function during CPB weaning. While our results may not be completely conclusive, they suggest that intraoperative myocardial recovery did not differ among the three groups.

Myocardial damage after reperfusion is also reflected in early postoperative outcomes. During the period of our study, we did not observe any significant perioperative myocardial infarction in procedures treating aortic stenosis. Therefore, the routine surveillance of cardiac biomarkers was not included in our postoperative management. This fact was also reflected in the present retrospective study. Instead, we collected postoperative data focusing on three major results of poor myocardial protection: low cardiac output syndrome, significant postoperative arrhythmias, and operative mortality. Our data

demonstrated no differences among the three groups in the incidence of low cardiac output syndrome and significant postoperative arrhythmias, and we noted a relatively low incidence compared to previous studies [1,7,8,13,16]. Surprisingly, no operative mortality was observed among the three groups. Moreover, no statistically significant differences were found among the three groups regarding other parameters that reflect early postoperative outcomes, such as ventilator support, duration of stay in the intensive care unit, and duration of stay in the hospital. These findings are in agreement with previous studies [6-8,13,16,17]. As well, no significant differences were found regarding long-term mortality. The Kaplan-Maier survival curves of overall mortality (Fig. 1) and freedom from cardiac related mortality (Fig. 2) showed no statistical significance. Further study is needed to confirm these conclusions.

The study has some potential limitations. First, some significant differences were found among the three groups regarding preoperative patient characteristics. The mean age of patients in groups B and C was higher than that of patients in group A. Group B included significantly fewer New York Heart Association III or IV patients compared to group C, according to the Bonferroni correction (group A versus group B, p=0.121; group A versus group C, p=1.00; group B versus group C; p=0.048). Moreover, patients in group C had higher EuroSCOREs, N-terminal pro-brain natriuretic peptide levels, and left ventricular mass index values. These results may reflect the recent presentation of relatively older patients and the inclusion of AR patients in group C. Matching the preoperative patient characteristics was not possible due to the retrospective nature of the study and the relatively small number of patients who were included. The second limitation is that data regarding perioperative cardiac biomarkers were not included in this study. Although our primary goal was to compare the clinical results of each method, the lack of data regarding perioperative cardiac biomarkers may have prevented the detection of perioperative myocardial ischemia.

In conclusion, although patient characteristics showed some differences among the three groups, antegrade crystalloid cardioplegia using HTK solution and retrograde cold blood cardioplegia alone provide similar early and late clinical results compared to the conventional method that combines antegrade and retrograde blood cardioplegia. These results need to be verified by further prospective studies involving larger populations to confirm their clinical relevance.

CONFLICT OF INTEREST

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

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