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ORIGINAL ARTICLE

Outcome of concomitant surgical treatment in patients with coronary artery disease and severe aortic stenosis: A single-center study

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Abstract

Background

Combined aortic valve replacement (AVR) and coronary artery bypass grafting (CABG) is mostly performed for patients with aortic stenosis (AS) and coronary artery disease (CAD).

Objectives

We aim to clarify that combined operation of AVR and CABG with adequate perioperative cardiac protection does not increase operative and postoperative risk.

Methods

A total of 217 patients who underwent AVR for aortic stenosis alone or combined AVR and CABG from 1/2002 to 12/2015 were recruited. The aortic valve alone group (group A) had 164 patients, with an average age of 71.6 ± 8.1 years. The combined operation group (group C) consisted of 54 patients, with an average age of 73.5 ± 8.5 years. Aortic valve area and pressure gradient showed no significant differences between the two groups. In group C, an average of 2 ± 0.8 vessels had CAD. Cold crystalloid cardioplegia according to left ventricular mass ± a terminal hot shot was used for all patients. Distal graft anastomosis was done after cardiac arrest and cardioplegia (1.5-fold normal) was injected additionally from the graft with severe proximal obstruction of the right coronary artery.

Results

Group C included more patients with diabetes mellitus (DM, 43.4% vs. 26.8%) and low left ventricular ejection fraction (LVEF<50%, 33.96% vs. 16.46%) than group A. On the other hand, the incidence of atrial fibrillation (AF, 3.77% vs. 13.41%) was significantly less in group C than in group A. Although cardiac arrest time was longer in group C, postoperative CPK-MB was not significantly elevated, except in 4 patients. Postoperative data showed no significant differences between the two groups.

Conclusions

In our department, satisfactory clinical outcomes were obtained with combined operation AVR and CABG. Sufficient myocardial protection had an important effect on clinical outcomes.

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Key words: aortic stenosis; aortic valve replacement; coronary artery disease; coronary artery bypass grafting; combined operation.

Introduction

Patients with aortic stenosis (AS) combined with coronary artery disease (CAD) are increasing with the increasing aging of society[1]. Patients with this condition require both aortic valve replacement (AVR) and coronary artery bypass grafting (CABG).

Previous studies showed that patients with AS had a CAD prevalence of 37%, and patients above 70 years of age had a CAD prevalence of over 50%[2, 3]. To obtain the best clinical outcomes, patients must undergo combined operation (CO) of AVR and CABG. However, AS patients with CAD always have worse conditions than isolated AS patients. According to recent reports[4, 5], CO increased operative mortality compared with isolated AVR.

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This strong association between AS and CAD is thought to be the common pathophysiology, including the low-density lipoprotein-mediated inflammatory response resulting in an accelerated atherosclerotic process[6]. AS and CAD patients have many of the same risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, smoking, higher serum osteoprotegerin, and so on[7, 8]. In these cases, it is a challenge for cardiovascular surgeons to obtain better clinical outcomes.

In this retrospective clinical study, the preoperative, operative, and postoperative factors of AS patients with and without CAD were compared to verify the hypothesis that combined operation of AVR and CABG with adequate perioperative cardiac protection does not increase operative and postoperative risk.

Methods and Operations

From January 2002 to December 2015, 289 patients underwent AVR for AS at Hirosaki University Hospital. Of these patients, 164 who underwent isolated AVR (group A) and 53 who underwent combined AVR and CABG (group C) were compared. Patients with previous cardiac surgery, re-do AVR, or other surgical procedures such as mitral valve repair were excluded. In all patients, aortic valve condition was assessed by transthoracic echocardiography. Aortic valve area less than 1.0 cm^2 and pressure gradient more than 50 mmHg were diagnosed as severe AS, which was calculated by doppler ultrasound. CAD was assessed by coronary angiography, and stenosis greater than 75% was considered significant. Informed consent was performed before operation for all patients. This retrospective study was approved by the institutional review boards of the Hospital of Hirosaki University (No. 2017-1037).

St. Thomas' II cardioplegic (CP) solution (Myotector, Mochida Pharmaceutical Co., Tokyo, Japan) was cooled to 4°C before perfusion, the amount of which was calculated according to patients' weight (10-20 mL/kg) and corrected body surface area. After the aorta was clamped, CP solution (20 mL/kg) was first administered antegrade when aortic regurgitation was absent or mild. Selective CP solution (10 mL/kg) was administered via a coronary artery ostium every 30 minutes after the first injection. Interventricular septal thickness (IVST) was measured to evaluate the heart weight of AS patients. The data showed that the IVST of AS patients was 1.02-1.65-fold the standard value. According to these data, CP solution was injected at 1.5-fold the normal dose from the second time for AS patients. In group C, in addition to selective antegrade cardioplegia, CP solution was administered additionally via the anastomosed bypass graft if the coronary artery had severe proximal stenosis or total obstruction. If cardiac arrest time was over 180 minutes, terminal warm blood cardioplegia (TWBC, 10 mL/kg) was used from the aortic root cardioplegia cannula before de-clamping of the aorta. Regarding body temperature management, mild hypothermia induced by natural cooling was used, while for patients on hemodialysis, moderate hypothermic cardiopulmonary bypass was used.

The pressure gradient through the aortic valve was assessed by transthoracic echocardiography, and in group A, AS was severe in 155 patients, moderate in 7 patients, and mild in 2 patients. In group C, AS was severe in 47 patients, moderate in 5 patients, and mild in 1 patient. All patients underwent AVR with a biological or mechanical valve (181:37) according to the patients' age and preference. A sufficient effective orifice area was obtained with the least pressure gradient.

In group C, the average number of vessels with CAD was 2 ± 0.8, and 34 patients had stenosis of the left anterior descending coronary artery (LAD). The average bypass number was

1.7 ± 0.9. Distal anastomosis of LITA-LAD bypass was performed under cardiac arrest in 16 patients, whereas it was performed during beating under cardiopulmonary bypass (CPB) using an intracoronary shunt in 10 patients because of good cardiac function. Reversed autologous saphenous vein grafts (GSV) were used in 8 patients who were octogenarians or had a small LITA. Distal anastomoses of the circumflex system were performed under cardiac arrest.

Statistical analysis

All analyses were performed with KyPlot 5.0 (KyensLab, New York, NY). Continuous variables are expressed as means ± standard deviation (SD) or as medians (interquartile range), as appropriate. Categorical variables are reported as frequencies and percentages. Comparisons between continuous variables were performed with the Kruskal-Wallis H test, as appropriate. Categorical variables were compared with the χ^2 test. Differences in survival were calculated by Kaplan-Meier curve analysis, and survival rates are reported at 1, 3, and 5 years. Preoperative, intra-operative, and postoperative factors were compared between groups A and C. A p value less than 0.05 was considered to indicate significance. This study was approved by the Institutional Review Board at Hirosaki University, Graduate School of Medicine.

Results

The prevalence of diabetes mellitus (DM) was significantly greater in group C than in group A (Table 1). However, there were no significant differences between the two groups in age and sex distributions. In group A, the mean age was 71.6 ± 8.1 years, and there were 72 male and 92 female patients. In group C, the mean age was 73.5 ± 8.5 years, and there were 29 male and 24 female patients. Other preoperative risk factors did not differ between the two groups, except for cerebral vascular disease (CVD) and low left ventricular ejection fraction (LVEF<50%). In group C, 18 patients had low LVEF confirmed by transthoracic echocardiography, significantly more than in group A ($p<0.01$). The other preoperative hemodynamic parameters did not differ between the two groups, including aortic valve area and pressure gradient. Patients' Japan score and predicted complications score were higher in group C than in group A. The STS score (6.33 ± 3.63 vs. 3.95 ± 2.82) also showed the same results.

Operative times, CPB times, and aortic clamp times were significantly longer in group C than in group A (Table 2). Postoperative complications, such as low cardiac output syndrome (LOS), sepsis, renal insufficiency, myocardial ischemia, cerebral ischemia, prolonged ICU stay, and prolonged mechanical ventilation, showed no significant differences between the two groups (Table 2). In group C, only 4 patients showed that the postoperative MB form creatine kinase (CPK-MB) was elevated over 50 IU/L (Table 3). However, postoperative LVEF was not different between the two groups. Postoperative CPK-MB was not elevated in low LVEF patients with our cardiac protection solution (Table 4). Total cardioplegia dose was showed according to heart disease (Table 5).

Clinical outcomes of groups A and C

Compared to group A, hospital stay was significantly prolonged in group C. Hospital mortality showed no significant differences between the two groups (Table 2). One-year survival was 95.7% in group A vs. 95.6% in group C, 3-year survival was 90.2% vs. 89.0%, and 5-year survival was 78.5% vs. 82.0%, respectively; there were no significant differences between the two groups (Figure 1).

Table 1. Preoperative clinical data of the two groups

	Single AVR (A group)	AVR+CABG (C group)	P
N	164	53	
Age, years	71.6 ± 8.1	73.5 ± 8.5	p=0.1631
Male gender, n, (%)	72(43.9%)	29(54.7%)	p=0.1704
Hypertension, n, (%)	115(70.1%)	39(73.6%)	p=0.6292
Hypercholesterolemia, n, (%)	51(31.1%)	23(43.4%)	p=0.1006
Diabetes n, (%)	44(26.8%)	23(43.4%)	p=0.023
Smoking Habit, n, (%)	39(23.8%)	13(24.5%)	p=0.9177
Low left ventricular ejection factor (LVEF) <50%. n, (%)	27(16.4%)	18(33.9%)	p=0.0063
Aortic valve area (AVA, cm^2)	0.69 ± 0.25	0.74 ± 0.23	p=0.186
Pressure gradient, (mmHg)	80.42 ± 29.23	75.2 ± 31.21	p=0.0984
Cardiac index (CI), L/min	3.33 ± 4.3	2.84 ± 0.78	p=0.5435
Left ventricular end diastolic volume index (EDVI), ml/m^2	88.9 ± 35.2	85.9 ± 33.3	p=0.721
Left ventricular end systolic volume index (ESVI), ml/m^2	41.2 ± 26.2	37.3 ± 18.9	p=0.5148
Atrial fibrillation, n, (%)	22(13.4%)	2(3.8%)	p=0.0517
New York Heart Association	2.32 ± 0.82	2.43 ± 0.69	p=0.3869
Cerebral Vascular Disorder, n, (%)	25(15.2%)	17(32.1%)	p=0.0307
Treated coronary, n, (%)		53(100%)	
No 1 of coronary		17(32.1%)	
No 2 of coronary		19(35.9%)	
No 3 of coronary		17(32%)	
Coronary artery disease (CAD) number	0.2 ± 0.6	2 ± 0.8	p<0.001
Brain natriuretic peptide (BNP), pg/mL	522.6 ± 118.7	367.1 ± 73.9	p=0.4614
Albumin, mg/dL	4.1 ± 0.49	4.27 ± 1.46	p=0.2194
Chronic kidney disease (CKD) (Cr>2mg/dL), n, (%)	13(7.9%)	6(11.3%)	p=0.4473
Maintenance dialysis (HD), n, (%)	13(7.9%)	5(9.4%)	p=0.9526
Shock, n, (%)	12(7.3%)	3(5.7%)	P=0.6794
Japan score	4.01 ± 0.29	6.37 ± 1.23	p=0.0075
Japan score and complication score	20.19 ± 0.84	30.66 ± 1.87	p<0.001
Society of thoracic surgeons (STS) score	3.95 ± 2.82	6.33 ± 3.63	p<0.001
Emergency operation, n, (%)	8(4.9%)	5(9.4%)	p=0.2725

Discussion

Combined operation of AVR and CABG has been reported to provide better clinical outcomes than AVR alone for AS patients with CAD[25]. According to current AHA/ACC guidelines, about 49% of these patients need combined AVR and CABG[9]. Patients with AS and CAD have been reported to have more postoperative complications than patients with isolated AS[1]. Although a previous study showed that mechanical ventilation was significantly prolonged in patients who underwent combined operation of AVR and CABG, it was not a predictor of poor surgical outcome[10]. But hospital mortality was increased by the combined operation[26]. Several studies showed that preoperative mortality was not different between combined AVR

Table 2. Intra-operative and postoperative clinical data of the two groups

	AVR only (A group)	AVR+CABG (C group)	P
N	164	53	
Operation time, min	299.1 ± 110.8	417.7 ± 167.9	P<0.001
Cardiopulmonary bypass time, min	151.4 ± 69.8	197.7 ± 48.2	P<0.001
Aortic clamp time, min	108.6 ± 38.9	136.8 ± 39.9	P<0.001
Aortic clamp, n, (%)	159(97%)	52(98%)	p=0.6538
Terminal warm blood cardioplegia, n, (%)	0	4(7.5%)	P<0.001
Circulation arrest, n, (%)	12(7.3%)	6(11.3%)	p=0.3796
Ventilation time, hour	17.1 ± 51.39	21.7 ± 33.76	p=0.5268
ICU stay, day	2.93 ± 2.67	3.79 ± 4.9	p=0.1104
Stroke, n, (%)	6(3.7%)	2(3.8%)	p=0.6222
Atrial fibrillation, n, (%)	59(35.9%)	18(33.9%)	p=0.4044
Continuous hemodiafiltration (CHDF), n, (%)	7(4.3%)	3(5.7%)	p=0.6949
Pneumonia, n, (%)	4(2.4%)	0(0%)	p=0.2467
Intro-aortic ballon pumping (IABP), n, (%)	3(1.8%)	3(5.7%)	p=0.1466
Hospital stay, day	21.4 ± 10.5	25.3 ± 13.0	p=0.0343
Postoperative mortality , n, (%)	3(1.8%)	2(3.7%)	p=0.4248
Long-term mortality, n, (%)	25(15.2%)	10(18.9%)	p=0.9428

Table 3. Myocardial protection of patients with postoperative increasing MB form creatine kinase (CPK-MB)

Case	Operation	Noradrenaline	Postoperative CPK-MB (IU/L)	Total cardioplegia solution (ml)	Times
1	AVR CAB3 (LITA-LAD, GSV-LCX, GSV-RCA)	+	162	3600	5
2	AVR CAB1(GSV-LAD) AAR	+	104	2250	4
3	AVR CAB1(GSV-LCX)	+	90	3250	4
4	AVR CAB1(GSV-RCA)	+	162	2500	4

AVR: Aortic valve replacement
AAR: Ascending aortic replacement
LITA: Left internal thoracic artery
GSV: Great saphenous vein
LAD: left anterior descending artery
LCX: Left circumflex artery
RCA: right coronary artery

and CABG and AVR alone, but operative-related morbidity and the incidence of prolonged ventilation were significantly higher with the combined operation[11, 12]. However, ventilation time was not prolonged in the combined operation group in the present study, indicating that prolonged cardiac arrest time was not a risk factor for postoperative respiratory dysfunction.

The patients with moderate AS and CAD undergoing CABG alone had a higher rate of re-

Table 4. Postoperative MB form creatine kinase (CPK-MB) of low LVEF patients in the two groups

Case	Age (Y)	Male	Diagnosis	Operation	Preoperative LVEF (%)	Ascending aortic clamp Time (Min)	Postoperative CPK-MB (U/L)
1	75	F	AS	AVR	30	72	9
2	71	F	AS	AVR	37.1	96	211
3	78	M	AS	AVR	32	146	10
4	80	M	AS	AVR	32.5	104	12
5	75	F	AS, Paf	AVR, AAR	37.7	102	21
6	69	F	AS, AP	AVR, CAB1 (GSV-RCA)	33.9	174	14
7	83	F	AS, AP	AVR, CAB1(GSV-LAD)	35	141	8
8	60	F	AS, AP	AVR CAB3(LITA-LAD, GSV-LCX, GSV-RCA) AAR	32.1	172	4
9	66	M	AS, AP	AVR CAB1(GSV-RCA)	30.6	123	6

Paf: Paroxysmal atrial fibrillation
AP: Angina pectoris
AVR: Aortic valve replacement
AAR: Ascending aortic replacement
F: Female
M: Male
LITA: Left internal thoracic artery
GSV: Great saphenous vein
LAD: left anterior descending artery
LCX: Left circumflex artery
RCA: right coronary artery

Table 5. Total cardioplegia dose.

Case	Weight(kg)	Total cardioplegia dose (ml)	Cardioplegia (ml/kg)
MR (MVP)	50	1000+500+500+500=2500	50
AS (AVR)	55.9	1650+830+830+819=4129	73.8
AS+CAD (AVR+CAB 3)	76.7	2400+1200+1060+930+1075=6665	86.8

MR: mitral regurgitation
AS: aortic stenosis
CAD: coronary artery disease
MVP: mitral valve plasty
AVR: aortic valve replacement
CAB: coronary artery bypass grafting

operation for AVR within 5 years postoperatively. Therefore, patients with moderate AS and CAD need combined AVR and CABG in the early phase[13]. Combined AVR and CABG for patients with moderate AS and CAD more than 70 years old should be positively performed if there are no additional preoperative risk factors[14]. Concomitant AVR at the time of CABG appears to convey a survival advantage for patients with moderate aortic stenosis[15].

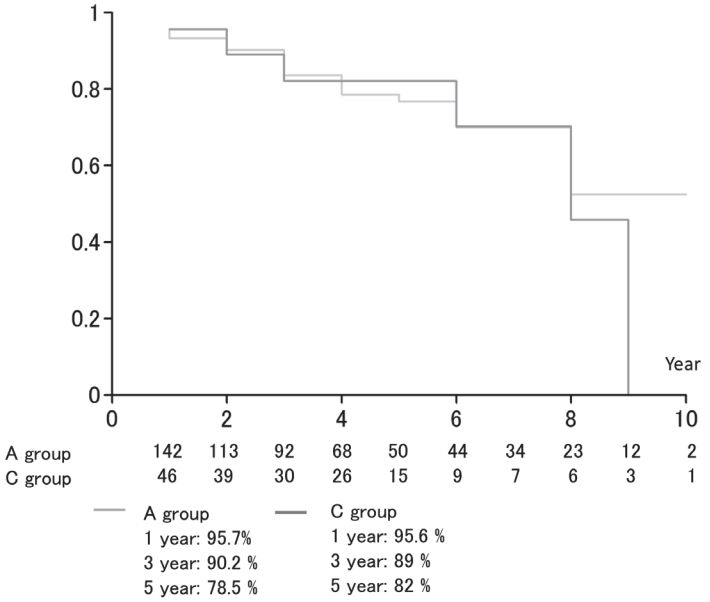

Figure 1 Long-term survival curves

In patients with low LVEF (less than 40%), New York Heart Association (NYHA) functional class of III or IV, chronic obstructive pulmonary disease (COPD), or renal failure preoperatively, long-term survival was significantly decreased[11]. Recently, transcatheter aortic valve replacement (TAVR) has been introduced into clinical use for severe AS patients who cannot tolerate conventional AVR. Although open AVR resulted in good clinical outcomes, TAVR for intermediate risk patients showed lower midterm mortality than surgical AVR[10, 16, 17]. The indications for TAVR in AS have been extending beyond high-risk patients recently, so we should consider combined TAVR and CABG or PCI and TAVR as an alternative to concomitant AVR and CABG for patients with AS and CAD in the future.

Previous studies showed that CABG performed with AVR could offset the adverse effect of CAD in patients with AS and CAD[18, 19]. Patients who underwent combined AVR and CABG showed longer cardiopulmonary bypass time and aortic clamp time than isolated AVR. Therefore, myocardial protection is the most important issue. Antegrade coronary artery cardioplegia perfusion is mostly and safely used, but retrograde perfusion from the coronary sinus is a safe and effective means of cardioplegia in aortic valve operations[20]. Cold blood cardioplegia reduces the increase in cardiac enzyme levels compared with cold crystalloid cardioplegia in patients undergoing isolated AVR[21]. Antegrade crystalloid cardioplegia and retrograde cold blood cardioplegia led to early and late clinical results similar to those achieved with combined antegrade and retrograde cold blood cardioplegia[22]. Continuous retrograde blood cardioplegia is associated with a good postoperative outcome in heart valve operations[23]. Terminal warm blood cardioplegia improved the recovery of myocardial electrical activity after coronary artery re-perfusion[27]. However, there is no standard solution and enough evidence as a reference. If patients need complicated bypass grafting to coronary arteries, we will consider to perform retrograde cardioplegia to protect from endocardial ischemia in our department.

When AS patients have CAD, and it becomes more difficult to obtain enough myocardial pro-

tection. A previous study showed that postoperative elevation of CPK-MB was found in many patients undergoing combined AVR and CABG[24]. In our department, we usually used cooled St. Thomas' II cardioplegic solution that was antegradely administered without blood first when aortic regurgitation was absent or mild. Advanced AS induces myocardial hypertrophy and endocardial ischemia, and we injected additional cardioplegic solution from the bypass graft to the right coronary artery, and we increased the quantity of cardioplegic solution according to the degree of hypertrophy assessed by preoperative echocardiography. When cardiac arrest time was over 180 minutes, we used terminal warm blood cardioplegia before staring coronary re-perfusion. Cold blood cardioplegia was not used, but retrograde coronary sinus cardioplegia was performed for patients when myocardial protection was insufficient or with complicated bypass grafting. We speculated that hypothermia and hyperkalemia were the most important factors for myocardial protection, so we used cooled crystal cardioplegia not mixed with cold blood, which was not sufficient due to decreased potassium and pH changes. Although we did not measure the temperature of the myocardium, it was decreased by cold cardioplegia during surgery. In order to sustain cooling and the arrest of the myocardium sufficiently, cold cardioplegic solution was injected every 30 minutes with 1.5 fold of normal dose. Bypass grafting was performed in heart arrest including LITA-LAD anastomosis, because beating anastomosis is not good for myocardium protection. Only 4 patients were found to have slight elevation of CPK-MB postoperatively by these efforts in group C, and low LVEF patients did not show increased postoperative CPK-MB, myocardial protection according to our protocol was sufficient.

Conclusions

Combined AVR and CABG could be performed safely with sufficient myocardial protection. Sufficient myocardial protection during cardiac arrest decreases myocardial ischemia and in-hospital complications, and has an important effect on increasing long-term survival.

Disclosure Statement

There are no disclosures.

Author Contributions

Study conception: ZY, KD
Data collection: ZY, KD
Analysis: ZY, KD
Investigation: ZY, KD
Writing: ZY, KD, IF
Funding acquisition: None
Critical review and revision: All authors
Final approval of the article: All authors
Accountability for all aspects of the work: All authors

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