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Antegrade Versus Simultaneous Ante/Retrograde Cardioplegia in the Presence of Three Vessels Disease

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This study was performed to compare myocardial cell injury and the rate of reduced cardiac ejection between antegrade vs antegrade/retrograde approach to myocardial preservation. All 208 3VD patients were categorized randomly in 2 groups containing 104 cases which underwent urgent or elective Coronary Artery Bypass Grafting (CABG) with Cardio Pulmonary Bypass (CPB). The cardioplegia method in group 1 was antegrade and in group 2 was ante+retrograde. The preparation of cardioplegin solution was the same in both groups. The levels of creatine kinase MB in 3, 12 and 36 h after operation was not significantly different between two groups but were higher than normal. Also, the levels of Cardiac Troponin I in 3 and 12 h after operation was not significantly different between two groups but were higher than normal. The higher MI rate in group 1 (8 cases) than group 2 (3 cases) can be considered significant clinically but this difference was not statistically significant. There was not significant difference between the mortality between group 2 (0 case) and group 1 (1 case). The number of Intra-aortic balloon pump insertion in both groups was the same. The time of aortic clamping and pump time was not different significantly between two groups. Although postoperative EF was decreased in both groups, this decrease was much higher in group 1 especially in those with severe (90% or complete cut) LAD and RCA lesions. We concluded that there is no significant preference among antegrade and antegrade/retrograde approach to myocardial preservation.

Key words: Antegrade cardioplegia, myocardial protection, retrograde cardioplegia

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INTRODUCTION

The aim of myocardial protection is to provide optimal physiological preservation of the cardiac myocardium allowing corrective surgical repairs. Favorable outcomes with respect to postoperative ventricular function are in large part dependent on optimal intraoperative myocardial protection (Allen *et al*., 2003; Yilik *et al*., 2004).

One of important issues in heart surgeries with Cardio Pulmonary Bypass (CPB) is the technique of cardiac protection. Since the first description of survival after cardiopulmonarybypass, improved myocardial preservation during periods of absentcoronary perfusion has been the goal of many research efforts. The vast majority of basic and clinical studies in myocardial preservation techniques for cardiac surgery have focused on different mechanisms for cardioplegia delivery, the temperature of the solution and substrate additives to the cardioplegic solution (Fazel *et al*., 2004; Cohen *et al*., 1999).

Early cardioplegic techniques relied on cold crystalloid to initiate and maintain intraoperative cardiac arrest. However, blood cardioplegia facilitates myocardial aerobic metabolism, preserves myocardial high-energy phosphate stores and reduces lactate production compared with crystalloid cardioplegia. Enhancement of cardioplegia using metabolic substrates such as glutamate has also been shown to improve metabolic recovery. Other alternatives include retrograde and/or antegrade delivery, continuous versus intermittent cardioplegia and the use of warm (37°C) or tepid (29°C) induction of cardioplegic arrest and/or a terminal infusion of warm blood cardioplegia to facilitate a return to aerobic metabolism (Mallidi *et al*., 2003; Kalawski *et al*., 2003; Flack *et al*., 2000; Dar MI., 2005; Licker *et al*., 2005).

The multiplicity of cardioplegic solutions available, their method of delivery, patient selection and the methods used to determine myocardial injury have made it difficult to accurately determine which form of cardioplegia is best (Cohen *et al*., 1999).

Our goal was to evaluate the homeostasis of myocardium during antegrade cardioplegia vs. simultaneous antegrade and retrograde crystalloid cardioplegia. We want to find out whether exclusive use of antegrade cardioplegia can provide adequate myocardial protection in three vessels disease patients.

MATERIALS AND METHODS

This is a clinical trial performed over 216 randomized patients with three coronary vessels disease (3VD) which were candidate for CABG. These patients had been referred by cardiologists for elective and urgent CABG to cardiac surgeons of Tabriz Shahid Madani Heart Center. The patients enrolled between August 14, 2003 and April 30, 2005.

Criteria for enrollment in the CABG Patch Trial included the following: age <80 years, presence of 3VD, homodynamic stability, absence of history of MI in recent week, absence of chest pain in 24 h before operation and elective and urgent operation.

Patients were excluded if they had a history of sustained ventricular tachycardiaor fibrillation, chest pain before operation, ECG changes such as ST elevation, the history of MI in recent week, IABP before operation, abnormal cardiac enzymes in preoperative tests, complication in Cath. Lab (acute obstruction, cardiogenic shock,…), diffused atherosclerosis and endarterectomy and incomplete revascularization during operation and emergent and salvage surgery, recurrent infections, concomitant cerebrovascular surgery, a serum creatinine concentration>3 mg dL^{-1}, emergency operation, or a noncardiovascular condition with expected survival of <2 years.

The rout of cardioplegin administration was selected randomly for induction of cardiac arrest. Retrograde method was performed for 108 patients (group 1) and ante+retrograde method were considered for remaining 108 patients (group 2). The patients in each group were matched according the type of operation, concomitant valve replacement and left main stem lesion.

Median sternotomy was done in all patients. A total Cardio Pulmonary Bypass (CPB) was established using bicaval cannulation with snaring and ascending aortic return. The left ventricle was drained with a sump catheter via the right superior pulmonary vein. Moderate systemic hypothermia (rectal temperature, 27° to 32°C) and hemodilution (hematocrit, 20 to 25%) were maintained during CPB.

A crystalloid cardioplegic solution, which is a sterile nonpyrogenic, isotonic formulation of water for injection, was used.

After cross clamping the aorta, cardiopleginwas given via a size-14 French cannula with a smoothself-inflating retention balloon. This resulted in a rapid diastolic arrest of the heart within 30 to 50 see.

The initial dose of cardioplegin in group 1 was 10 cc kg^{-1} followed by maintenance dose of 5 cc kg^{-1} repeated every 20-30 min. The potassium level in initial and maintenance doses of cardioplegin was the same (20 meq L^{-1}).

The initial dose of cardioplegin in group 2 was 10 cc kg^{-1} of which 5 cc kg^{-1} was injected antegradely and 5 cc kg^{-1} was injected retrogradely (through coronary

sinus). The initial dose was followed by maintenance dose of 5 CC kg^{-1} which was injected retrogradely every 20-30 min.

The total dose of cardioplegin in both groups was the same. After termination of surgery, reperfusion was established by opening the aortic clamp for 2 min with pressure <30 mmHg. Anesthesia and termination of CPB in both groups was the same.

Coronary artery bypass grafting (CABG) was done during single aortic cross clamping. Concomitant procedures if any (valve repair and/or replacement), were carried out. As the patients were rewarmed to normothermia, 1 L of warm (35° to 37°C) cardioplegia was given retrograde just before removing the aortic cross clamp. Patients were weaned off CPB and the operation was concluded.

Basic 12 leads ECG were performed in the surgery morning. ECG was repeated a day after surgery in ICU and followed by daily ECG to 5 days. Cardiac enzymes (CKMB and troponin I) were measured in 3, 12 and 36 h after operation (Table 3).

The patients were visited daily by a cardiologist until discharge from ICU. The presence of postoperative MI were excluded or confirmed by cardiologist according to the hemodynamic status, ECG, cardiac enzymes or (if needed) echocardiography. In both groups, the presence of elevated ST and subsequently newly appeared Q wave with raised CKMB more than 30 μL^{-1} and Troponin I to 10-20 times of normal value was considered as MI. other variables (pump duration, clamping time and IABP placement) were recorded.

Statistical analysis: The collected data were analyzed by SPSS-12 statistical software. We used student T-test and Chi-square test for comparison of quantitative and qualitative data, respectively between 2 groups. Paired T-test was used for comparison of LVEF variables before and after operation. The p-values more than 0.05 were considered significant. Data are presented as Mean±SE for continuous variables in Tables.

RESULTS

None of 216 studied patients underwent emergent or salvage operation. All of them were candidate of elective CABG, had not chest pain 24 h before operation and their hemodynamic status before operation were stable.

According to the Table 1, the demographic characteristics of patients before operation and their risk factors was not significantly different ($p<0.05$).

According to the Table 2, only LVEF is lower in group 2 ($p = 0.07$). However, average LVEF in both groups was in the range of moderate LV dysfunction (30-50%), indicating the same risk level in both groups. Table 3 shows the postoperative LVEF and levels of CK and Troponin I enzymes in various h after operation, MI rate, mortality and the need for IABP following CABG. As showed in Table 3, postoperative LVEF is not significantly different in both groups ($p = 0.182$). the biomarkers and chemical parameters including Troponin I in 3 and 12 h after operation and CKMB in 3, 12 and 36 h following operation were not significantly different in both groups ($p<0.05$) but was elevated than normal levels.

Also, MI, mortality, IABP replacement, aortic clamping time and pumping time during operation were not significantly different in both groups ($p<0.05$).

Table 4 shows the pre- and postoperative LVEF in patients with≥90% lesions or complete cut off.

Paired t-test showed that according to the Table 4, postoperative LVEF in patients with involvement of LAD (left anterior descending) and RCA (right coronary artery) is significantly lower than preoperative LVEF. Also, this difference between patients with LAD and RCA disease in group 1 (5% reduce in LVEF) and group 2 (2.7% reduce in LVEF) was significant ($p<0.05$).

Table 1: The characteristics of studied patients and their risk factors for CAD

Variable	Group 1	Group 2	p-value
Age (year)	57±10	59±11	0.077
Sex ratio (male/female)	85/23	81/25	0.812
Weight (kg)	73±13	72±12	0.795
Diabetes mellitus	19	23	0.060
Hyperlipidemia	42	40	0.888
Hypertension	49	41	0.334
Smoking	44	43	1.000
Family history	11	11	1.000

Table 2: Comparison of the disease severity before operation between two groups

Variable	Group 1	Group 2	p-value
LAD average stenosis	84.24±13.20	86.76±16.46	0.215
LCX average stenosis	79.25±12.61	81.48±17.17	0.278
RCX average stenosis	85.37±14.72	82.057±17.95	0.212
Preoperative LVEF	47.22±9.70	44.26±9.72	0.027

Table 3: Comparison of enzymatic changes, postoperative complications, aortic clamping time and pumping time between two groups

Variable	Group 1	Group 2	p-value
Average postoperative LVEF	42.40±7.85	40.88±8.65	0.182
Average CKMB 3 h after operation	49.73±51.12	50.57±24.69	0.880
Average CKMB 12 h after operation	50.76±40.24	49.43±27.11	0.079
Average CKMB 36 h after operation	39.93±25.48	47.35±30.62	0.778
Average cTroponinI 3 h after operation	4.19±11.19	6.32±26.80	0.456
Average cTroponinI 12 h after operation	4.32±10.91	3.46±3.16	0.449
Postoperative MI	8	3	0.12
Postoperative IABP placement	7	6	1.000
Mortality (number)	1	0	0.614
Aortic clamping time (min)	77.58±18.134	66.99±17.58	0.192
Pump duration (min)	114.54±30.66	122.75±30.36	0.055

Table 4: Comparison of preoperative and postoperative LVEF in patients with≥90% lesions or complete cut off

	Group 1			Group 2		
Variable	Postoperative LVEF	Preoperative LVEF	p-value	Postoperative LVEF	Preoperative LVEF	p-value
LAD	47±9	41±8	0.0001	43±10	41±9	0.021
LCX	45.6±10	42±7	0.042	42±10	39±9	0.017
RCA	46±10	41±8	0.0001	43.7±10	41±8	0.01

Table 5: Comparison of postoperative complications in patients with≥90% lesions or complete cut off in each group, regarding the involvement of LAD, LCX, or RCA coronary arteries

Variable		ST elevation	MI	Mortality
LAD	Group 1	9	6	0
	Group 2	4	1	0
	p-value	0.252	0.048	
LCX	Group 1	4	3	0
	Group 2	1	1	0
	p-value	0.365	0.317	
RCA	Group 1	4	5	0
	Group 2	1	1	0
	p-value	0.365	0.252	

Table 6: Comparison of mortality, myocardial infarction (MI) and the need for IABP in patients with left main stem lesion and patients underwent concomitant aortic or mitral valve replacement and CABG

Variable		Left main stem lesion	CABG+Valvereplacement
Mortality	Group 1	1	0
	Group 2	0	1
	p-value	1.000	1.000
Acute MI	Group 1	2	1
	Group 2	2	0
	p-value	1.000	1.000
IABP placement	Group 1	2	1
	Group 2	0	1
	p-value	0.465	1.000

However, the difference of LVEF before and after operation in patients with involvement of LCX (left circumflex) artery was not significant. Also, this difference between patients with LCX disease in group 1 and group 2 was not significant ($p>0.05$).

Table 5 represents the comparison of postoperative complications in patients with≥90% lesions or complete cut off in each group, regarding the involvement of LAD, LCX, or RCA coronary arteries.

Sixteen patients in each group had left main stem lesion and 5 patients in each group underwent concomitant replacement of aortic or mitral valve. Mortality, acute perioperative MI and the need for IABP in these patients have shown in Table 6. In addition to data presented in Table 5, the enzymatic and LVEF changes in both groups were not significantly different ($p>0.05$).

DISCUSSION

Previously, the antegrade perfusion of cardioplegin solution was preferred method of most heart surgeons. Despite of great clinical and practical successes, this method has an essential limitation in myocardial preservation. Myocardial areas distal to complete coronary artery occlusion are poorly protected by antegrade cardioplegia (Jasinski *et al*., 1997).

Studies showed that in the presence of coronary artery occlusion or stenosis, retrograde delivery of cardioplegic solution results in a better preservation of myocardial energy reserve than antegrade delivery (Jasinski *et al*., 2000; Karthik *et al*., 2004). Retrograde cardioplegia through the coronary sinus provides more uniform distribution of cardioplegic solution (Kalawski *et al*., 2003).

Iannettoni *et al* examined the functional and metabolic indices of regional myocardial preservation following acute coronary occlusion with evolving ischemia in a canine model. Although only moderate reduction of global function was seen with Retrograde Cardio Plegia (RCP), the severe reduction noted in Left Anterior Descending artery (LAD) regional wall motion with Antegrade Cardio Plegia (ACP) reflects poor regional protection that can be significantly improved in evolving ischemia with RCP (Iannettoni *et al*., 1995).

However, it has been suggested that the right ventricular myocardium is suboptimally protected during retrograde blood cardioplegia (Kaukoranta *et al*., 1998). Care should be taken when retrograde normothermic blood cardioplegia is provided for patients with right ventricular hypertrophy, poor right ventricular function, or severe preoperative myocardial ischemia (Kaukoranta *et al*., 1998).

Some studies suggest that the route of cardioplegia administration is not a determinant of clinical outcome (Karthik *et al*., 2004). Yoshimasa *et al*. (2000) conducted a study on two group of candidate for CABG. These patients were matched regarding the age, preoperative EF and severity of coronary artery disease. They obtained the same results from antegrade and retrograde perfusion of cardioplegic solution. Present study also showed that the postoperative LVEF was not significant between two groups.

Jasinski *et al*. (1997) suggest that retrograde cardioplegia reduces ischemic injury and permits better early recovery of myocardial function. There is no difference, however, regarding long-term assessment of myocardial recovery.

Other studies suggest that metabolic viability of myocardium measured with oxygen utilization is better preserved with simultaneous antegrade and retrograde

cardioplegia (Jasinski *et al*., 2000; Gates *et al*., 1996). Many surgeons now use a combination of antegrade and retrograde perfusion (Kalawski *et al*., 2003). Gates *et al*. (1996) suggest that antegrade cardioplegia alone does not perfuse all available myocardial capillaries and that the addition of retrograde cardioplegia enhances overall microvascular distribution and perfusion.

The efficacy of intraoperative myocardial protection may be assessed clinically by: 1. operative mortality; 2. prevalence of intra-or perioperative myocardial infarction, suspected clinically and confirmed by electrocardiographic or enzymatic evidence; 3. requirement of IABP or inotropic support at the time of leaving the operating room and 4. significant ventricular arrhythmias and conduction disturbances post bypass and in the perioperative period (Talwalkar *et al*., 1999).

Cardiac marker elevation is universal after cardiac surgery. The standard biochemical marker for detection of perioperative necrosis is continuous creatine kinase subfraction MB (CK-MB) measurement but its specificity and sensitivity is limited. Cardiac troponins (cTnT, cTnI) are superior to CK-MB for the prediction of impending complications after cardiac surgical procedures (Januzzi *et al*., 2002; Guerin *et al*., 2006). Troponin I has complete cardiospecificity and is clinically used for diagnosis of myocardial infarction in other settings. Postoperative variables have a stronger correlation with peak cardiac troponin I than peak CK-MB. Peak troponin I values detect myocardial infarction the day after heart surgery and predicts patient outcome (Greenson *et al*., 2001).

The study of Kaukoranta *et al*. (1998) showed that the maximum efflux of CK-MB and troponins is the same in both antegrade and retrograde groups. Also, a study by Francois *et al* showed that Peak enzyme (CK-MB and troponins) release at 24 h was similar in both antegrade and antegrade/retrograde groups (Francois *et al*., 1999). These finding are compatible with study results in which the difference of release of these markers in two groups was not significant.

Perioperative MI has an adverse effect on early and late prognosis. The reported incidence varies widely (0 to >10%), in large part due to heterogenous diagnostic criteria, with an average of 3.9% (median 2.9%) (Nalysnyk *et al*., 2003). In this study, perioperative MI was 8 cases (7.4%) in group 1 in comparison with 3 cases (2.8%) in group 2. This difference cab be considered significant clinically but is not statistically significant.

In this study, 16 patients of each group had left main stem disease. Mortality, perioperative MI and the need for IABP between these patients in two groups were not significantly different. The optimum route for cardioplegia administration in such patients with severe coronary disease is still under debate (Onorati *et al*., 2003). Onorati *et al* compared clinical, echocardiographic and biochemical results in patients with left main stem disease treated with 2 different strategies of myocardial protection. One hundred and forty eight consecutive patients were divided into 2 groups according to the route of cardioplegia delivery: antegrade in 87 patients (group A) or antegrade followed by retrograde in 61 patients (group B). Electrocardiography, troponin I, MB-creatine kinase and MB-creatine kinase mass were performed at 12, 24, 48 and 72 h postoperatively. Hospital deaths, intensive therapy unit and hospital stay, perioperative acute myocardial infarction and intraaortic balloon pump support were similar in both groups. Postoperative recovery of LVEF and wall motion score index did not differ between the 2 groups. They concluded that the combined route of intermittent blood cardioplegia allows better results in Left Main Stem Disease (LMSD). Such data are confirmed even in risk subgroups (Onorati *et al*., 2003). Onorati *et al*. (2005) conducted the other same study in diabetics with left main stem disease and concluded that despite major in hospital end-points did not differ with strategy of cardioplegia administration, combined route of intermittent blood cardioplegia allows better biochemical and perioperative results in diabetics with LMSD.

In this study 5 cases in each group had simultaneous coronary artery disease and valvular disease and all of them underwent concomitant CABG and valvular replacement. Mortality, perioperative MI and the need for IABP between these patients in two groups were not significantly different.

Francois *et al*. (1999) concluded that there is no significant advantage of the antegrade/retrograde administration of cardioplegia over the antegrade route in routine valvular replacement, other than a slightly shorter aortic cross-clamping time.

Studies show that most patients with severe mitral and aortic valve disease have Left Ventricular Hypertrophy (LVH). LVH increase the myocardial metabolic demand during ischemic arrest and increase the heart ischemia during cardiac surgeries. In addition, thickened ventricular septa in association with increased left ventricular end diastolic pressure causes more decrease in subendocardial perfusion. So, use of cardioplegic method which can protect the heart optimally is essential in patients undergoing valvular replacement surgeries (Francois *et al*., 1999).

Retrograde coronary sinus cardioplegia is an effective and safe method of cardioplegia delivery in valve operations. Its specific advantages in the presence of

aortic insufficiency and occluded left anterior descending coronary artery have been noted in previous reports (Talwalkar *et al*., 1999; Di Luozzo *et al*., 2005). Talwalkar *et al*. (1999) used retrograde cardioplegia exclusively in all valve operations (with concomitant procedures, if any) without prior antegrade cardioplegia and had good clinical outcome. Delay in the onset of diastolic arrests considered a disadvantage of using cardioplegia solely by the retrograde method, in contrast to rapid diastolic arrest achieved by antegrade method. However, this feature of retrograde method does not seem to have clinically detectable adverse effects on the operative outcome (Talwalkar *et al*., 1999; Lin *et al*., 2001). In addition, low operative mortality, absence of perioperativeMI and low, acceptable prevalence of ventricular arrhythmias/conduction disturbances and hemodynamic instability requiring inotropic support in the immediate perioperative period are the clinical markers indicative of adequate myocardial protection (Talwalkar *et al*., 1999).

CONCLUSIONS

This study shows that retrograde cardioplegia is better to performed as a complementary method and not as an exclusive approach. In addition to priority and superiority of retrograde method to antegrade method in acute and severe coronary syndromes, we had clinically significant reduction in perioperative MI in patients with LAD and RCA (>90% or complete cut) in retrograde method, although this difference was not statistically significant.

The maintenance of postoperative LVEF was in retrograde than antegrade method although this difference was not statistically significant.

However, the myocardial protection methods are steel suboptimal. In future cardiopreservation methods, controlled aortic root reperfusion should be considered seriously. Our patients had not controlled end-operative reperfusion and this can be the reason for absence of postoperative LVEF in both groups.

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