Does Retrograde Administration of Cardioplegic Solution Improve the Clinical Outcomes in Primary Coronary Artery Bypass Grafting?

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Abstract:

Background: The quality of myocardial protection during Coronary Artery Bypass Grafting (CABG) has a direct effect on post-operative cardiac function, recovery and complications. The optimal route for delivery of cardioplegia is still in debate in patients with ischemic heart disease. This prospective randomized clinical study was designed to assess and compare the use of combined antegrade-retrograde cardioplegia versus antegrade cardioplegia in providing adequate myocardial preservation during coronary artery bypass graft surgery.

Methods: A total number of 150 patients that underwent CABG between 2009 and 2010 were assigned randomly into two groups according to myocardial protection technique; 75patients were randomly assigned to receive antegrade cold blood cardioplegia (group A) and the other 75 patients received combined antegrade-retrograde cold blood cardioplegia (groupA/R). This prospective randomized study compared clinical, echocardiographic, markers of myocardial damage, morbidity and mortality in two groups.

Results: The two randomization groups had similar demographic characteristics. The number of grafted coronary arteries averaged 3.2±0.4 in group A and 3.3±0.4 in group A/R. Total duration of cardiopulmonary bypass (64.1±23.2 and 66.3±16 minutes) and aortic cross-clamping (36.9± 13.7 and 34.6±8.6 minutes) were similar in both groups. There was one death in group A and one in group A/R, for a global early mortality of 1.3%. The cause of death was free wall LV rupture in group A and respiratory failure and pneumonia in group A/R. Release of total creatine kinase, creatine kinase–MB and troponin T were not significantly different ($p > 0.05$) between the two groups.

The number of postoperative myocardial infarction (12% versus 8%), the need for inotropic support (17.3% versus 12%), the need for IABP (2.7% versus 1.3%), postoperative arrhythmias (4% in each groups) were similar in both groups ($P>0.05$). Re-exploration, stroke, pulmonary complication, renal failure and wound infections also were similar ($P>0.05$).

Conclusions: Our results indicate suggest that the retrograde cardioplegia administration essentially does not improve myocardial protection during the first operation for isolated coronary revascularization compared with the usual antegrade route. The data indicate that in this non-risk-stratified group of patients, the route of cardioplegia administration is not a determinant of clinical outcome.

Key words: Antegrade Cardioplegia, Myocardial Protection, Retrograde Cardioplegia. CABG

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Introduction:

Effective intraoperative myocardial protection requires adequate distribution of cardioplegic solution to all myocardial segments to be accomplished in a safe, simple,and rapid fashion (1). Nonhomogenous distribution of cardioplegia in severe critical proximal coronary artery stenosis and in evolving myocardial infarction has been demonstrated experimentally (2).

Perfusion of the heart through the coronary sinus, so-called retrograde perfusion, was originally proposed by Pratt in 1898 (3). In 1956, this technique was first used by Lillehei et al. during cardiac surgery for the protection of jeopardized myocardium because coronary atherosclerosis does not occur in the coronary venous system (3).

However the preferential way of giving cardioplegia for myocardial protection strategy in patients with severe coronary artery disease is still under debate. Some of cardiac surgeons suggest routine use of retrograde cardioplegia administration (2,4) and others prefer the antegrade route (5,6). This controversy arises due to the large amount of clinical, biochemical, and histological studies that have been performed during the last 2 decades(4). In human, retrograde cardioplegic solution is administered through the coronary sinus into the cardiac venous system. Most of the veins in the heart drain to the right atrium through the coronary sinus. However, a smaller part of the cardiac venous return drains directly to the cardiac chambers through the anterior cardiac veins and the thebesian veins (venae cordis minima), particularly in the right side (7).

Some studies indicate that combined antegrade-retrograde cardioplegia is superior to antegrade cardioplegia for myocardial protection during coronary artery bypass graft surgery (2,4,8). However, recent studies have documented that retrograde cardioplegia does not adequately perfuse the right ventricle. The possibility of delayed cardiac arrest due to the low flow rate used for retrograde cardioplegia has also been noted (9) and many studies have shown no clear advantage in myocardial protection of retrograde versus antegrade cardioplegia (10).

Our study was designed to determine if using combined antegrade-retrograde cardioplegia is associated with better clinical outcome than the usage of antegrade technique alone.

Materials and Methods:

A total number of 150 patients that underwent CABG between 2009 and 2010 were assigned randomly into two groups according to myocardial protection technique; 75patients were randomly assigned to receive antegrade cold blood cardioplegia (group A) and the other 75 patients received combined antegrade-retrograde cold blood cardioplegia (groupA/R).

After the patients had agreed to participate in the study and signed an informed consent form, assignment to one of the two treatment groups and randomization was done just before the beginning of the operation. Group allocation was blinded to the patient, using blocks of four for equal sample size in the two groups.

Patients with reoperations for myocardial revascularization and coronary operations associated with any other cardiac surgical procedures were excluded.

All procedures were performed by the same team. All the operations were performed via a median sternotomy and using cardiopulmonary bypass machine. Heparin was administered at a dose of 300 IU/kg to achieve a target activated clotting time of 480 seconds or greater. After aortic cannulation followed by two stage atrial cannulation, a 14F retrograde coronary sinus perfusion catheter with a manual-inflating balloon was inserted by palpation of the coronary sinus, just before restoration of (CPB) in the A/R groupe. If necessary, the catheter was repositioned until the middle cardiac vein was filled, when cardioplegic solution was administered. Cardiopulmonary bypass was instituted using moderate haemodilution with a haematocrit level of 20% to 25% and mild systemic hypothermia (nasopharyngeal temperature, 30-32 °C). Pump flows were 2.0 to 2.2 L/min/m2, and the mean arterial pressure was maintained between 50 and 60 mmHg, with administration of nitroglycerin or phenylephrine hydro-chloride as required.

The delivery system for cardioplegic solution was a Y-shaped line with stop-cock on the incoming limb which used for directing the cardioplegic solution antegrade to the aortic root (in both groups) or retrograde to the coronary sinus catheter in group A/R only. The temperature of the blood collected for blood cardioplegia solution was 4°C at a 4:1 blood: solution ratio. After cross-clamping the ascending aorta, we accomplished the induction of cardiac arrest in both groups by giving cardioplegic solution contained

blood (1000 mL), potassium (20 mEq/L), sodium bicarbonate (10mEq/L), and magnesium sulphate (6 mEq/L) delivered into the aortic root ,the whole liter in groupA and 2/3 liter in group A/R at a pressure of 60-100 mmHg in the aortic root, followed by coronary sinus infusion of the 1/3 liter (200 to 400 mL/min) at a pressure of 30-50 mmHg in the coronary sinus in group A/R. The maintenance solution contained blood (500 mL),potassium (10 mEq/L), and sodium bicarbonate (5 mEq/L) which was given with an antegrade infusion in group A and retrogradely through the coronary sinus in group A/R every 20 minutes. Cardioplegia was never given simultaneously by the two routes.

The left internal mammary artery (LIMA) was used for revascularization of the left anterior descending coronary artery, and saphenous vein grafts were used for the others. Proximal anastomoses were always performed with aortic partial clamping.

All data were collected in a prospective manner and were expressed as mean ± standard deviation (SD). Analysis of continuous variables was performed with Student's t-test, and that of repeated measures was performed with a 2-way analysis of variance test. Categorical variables were expressed as percentage and were compared by x2 statistical analysis. All analyses were performed using SPSS software, 2 versions 15 (SPSS, Inc. Chicago, IL). Results were considered significant when P values < 0.05.

Results

Both groups were comparable regarding the perioperative characteristics, as shown in Table (1). There was no significant difference between the two study groups in gender, age, body surface area , extension of the disease, pre-operative ejection fraction and comorbidities (diabetes, hypertension andCOPD).

Table 1. Preoperative Clinical and Angiographic Characteristics of the Patientsa

Characteristic	Antegrade Group (n =75)	antegrade-retrograde Group (n = 75)	P Value
Age (years)	60±9.4	61±8.8	0.45
Sex (M/F)	57/18	53/22	0.46
Height (Cm)	165.6±9	163±7.9	0.07
Weight (Kg)	72.7±13.2	70.1±11.9	0.19
BSA (m2)	1.8±0.19	1.75±0.16	0.08
Smoking	40 (53.3%)	36 (48%)	0.51
Opium usage	26 (34.7%)	23 (30.7%)	0.60
Hypertension	30 (40%)	27 (36%)	0.61
Hyperlipidemia	32 (42.6%)	43 (57.3%)	0.07
Diabetes	26 (34.7%)	20 (26.7%)	0.28
COPD	3 (4%)	2 (2.7%)	0.64
Left.main stenosis (>50%)	3 (4%)	3 (4%)	1
Urgent CABG	4 (5.3%)	5 (6.7%)	0.73
Pre op EF (%)	46.5±8.8	44.2±9.3	0.11
Pre op CPKMB	15.8±24.3	20.9±14.6	0.11
Preop. Troponin	0.19±0.37	0.26±1.6	0.70

There was no significant difference between the groups in regard to the number of bypassed vessels, duration of aortic cross-clamping, total cardiopulmonary bypass and total operation time (Table 2). With an average of 3.25 grafted vessels per patient, complete revascularization was achieved in all of the patients.

The biochemical markers for MI showed no statistical difference between groups in terms of Troponin sampling

from postoperative hours 12 and 24.
Total serum CPK activity and CPK MB sampling 1 and 24 hours postoperatively has no significant difference between groups (p>0.05). (Table 3).

Table 2. Comparison of Operative Data Between the Two Groupsa

Variable	Antegrade Group (n = 75)	Antegrade-Retrograde Group (n = 75)	P Value
Aortic cross-clamp time (min)	36.9 ±13.7	34.6 ±8	0.84
Duration of CPB	64.1 ±23.2	66.3 ±16	0.49
Duration of surgery	218.8 ±52.4	226.6 ±43.4	0.32
Grafted vessels per patient (no)	3.2 ±0.4	3.3 ±0.4	0.80

Table 3. Comparison of Postoperative Data Between the Two Groupsa

Variable	Antegrade Group (n =75)	Antegrade-Retrograde Group (n =75)	P Value
Troponin at 12 h	1.76 ±1.88	1.64 ±4.58	0.85
Troponin at 24 h	1.1 ±1.26	1.01 ±1.41	0.81
CPK at 1 h	451.8 ±436.9	92.3 ±10.19	0.07
CPK-MB at 1 h	48.6 ±24.7	50 ±57.67	0.85
CPK at 24h	841.9 ±798.6	1086.9 ±1252	0.15
CPK-MB at 24 h	58.1 ±52	48.8 ±40	0.22
Post operative EF	43.6 ±7.5	43.4 ±8	0.88
Mechanical ventilation time (hours)	12.4 ±13.3	10.8 ±22.2	0.59
ICU stay (day)	2.67 ±1.5	2.59 ±2.1	0.79
Hospitalization time (day)	7.6 ±2.5	7.8 ±2.6	0.58

There was no difference (p>0.05) in the in-cidence of postoperative myocardial infarction (12% versus 8%).
There was no significant difference in the need for pharmacologic(inotropic) or mechanical (IABP) support postoperatively.
Postoperative bleeding has no significant difference between groups .The incidence of mediastinal hemorrhage and tamponade that required surgical exploration was similar between groups.

The incidence of stroke, acute renal failure (ARF), pulmonary complications, arrhythmias, wounds infections was similar between groups. There were no complications from right ventricle dysfunction and ischemia.
There were no complications of retrograde cardioplegia catheter including rupture or perforation of the sinus, hematoma, and rupture of the catheter cuff.
Two hospital deaths (1 from each group) among 150 patients were noted (1.3 %). Both patients presented with preoperative MI and underwent urgent CABG. The cause of death was free wall LV rupture in group A and respiratory failure and pneumonia in A/R group (Table 4).
ICU stay, hospital stay and predischarge ejection fraction were similar in both groups.

Table 4. Comparison of Postoperative morbidity and mortality Between the Two Groupsa

Variable	Antegrade Group (n =75)	Antegrade-Retrograde Group (n =75)	P Value
MI	9 (12%)	6 (8%)	0.41
Need to Inotropes	13 (17.3%)	9 (12%)	0.35
Need to IABP*	2 (2.7%)	1 (1.3%)	0.56
Post op 24h bleeding volume(ml)	465±344	428±317	0.49
Reenploration	6 (8%)	2 (2.6%)	0.19
Stroke	1 (1,3%)	0	0.19
Renal failure	3 (4%)	1 (1.3%)	0.31
Pulmonary complications	10 (13.3%)	7 (9%)	0.19
Arrhythmias	3 (4%)	3 (4%)	1
Wound Infental	1 (1.3%)	4 (5.3%)	0.17
Mortality	1 (1.3%)	1 (1.3%)	1

*Intra aortic balloon pump

Discussion

Different strategies are used to keep the myocardium alive during on-pump coronary artery bypass grafting(4). Furthermore, there is no consensus on using an optimal method for the protection of myocardium during ischemic arrest, although it has been debated since the beginning of open heart

surgery (11). Myocardial protection during cardiac operations depends on adequate delivery of cardioplegia solution to all regions of the heart (12). The infusion of cardioplegic solution through the aortic root produces very quick diastolic arrest and good preservation of myocardial function. However, when advanced coronary disease is considered, it can result in an unequal distribution and consequently delayed functional recovery (13). It can be overcomed by coronary sinus cardioplegia, when the unobstructed coronary venous system can be used as a route for homogenous distribution (4,11)

Several clinical studies indicate that retrograde cardioplegia provides adequate myocardial protection in the human (15). Evidence of a more homogenous distribution of cardioplegia is suggested with the retrograde route (13). In the presence of complete coronary artery occlusion, this method would appear to result in a better perfusion of the ischemic myocardial area (12,11)

More recently, studies have shown that the right ventricular myocardium is poorly perfused with retrograde cardioplegic infusion in the human (16,17). Uneven distribution of cardioplegia administered through the coronary sinus has also been found in the experimental animal, confirming the findings of clinical studies that the right ventricle and posterior septum are particularly at risk (18,19).

These results have stimulated the use of combined antegrade and retrograde infusion of cardioplegia to alleviate the problem of uneven distribution (2, 4, 8). Shirai and colleagues found that myocardial function was better preserved with alternate compared with simultaneous antegrade and retrograde cardioplegic infusions, although the latter method was more practical with a lesser risk of coronary air embolism (20).

Michel Carrier, MD and colleagues and also Aurel C. Cernaianu, MD and colleagues showed that defibrillation attempts and spontaneous return to sinus rhythm, the use of intraaortic balloon pump counterpulsation, and inotropic support during weaning from cardiopulmonary bypass, were not statistically different between the two groups. The postoperative cardiac output, electrocardio-graphic and cardiac enzyme evidence of ischemia, the need for temporary pacing, and 30-day morbidity and mortality were similar for both groups.(10, 22)

In our study the two groups did not differ significantly in regard to their preoperative clinical and angiographic profile, surgical characteristics, and cardioplegic solution infusions other than the route of administration. None of the postoperative variables used as end points differed between groups.

In present study the incidences of elevated amounts of myocardial biomarkers were similar in both study groups, however, the rate of post-operative MI was lower in A/R group but this difference was not statistically significant. So it seems that the combined antegrade & retrograde route of cardioplegia infusion cannot improve the myocardial management at least in non-complex primary routine cases. Also there were no differences in early mortality and morbidity between the two groups.

Although the need for inotropic agents and intra aortic balloon pump after the procedures were lower in A/R group but this difference was not statistically significant.

A number of drawbacks were associated with retrograde perfusion, including coronary sinus rupture, myocardial edema) and right atrial conduction irregularities (14). The older techniques of retrograde perfusion required direct visualization of the coronary sinus and right atrial exclusion. However, a transatrial technique of retrograde perfusion through a balloon-tip catheter helps to simplify cannula insertion and to avoid injury both to the coronary sinus (by eliminating the need for purse-string sutures) and to the right atriutm (by reducing the need to manipulate it)(21). In the present study, there was no failure of retrograde cannulation (crossover to the antegrade group) and we did not have any coronary sinus catheter insertion complications.

In conclusion, although Retrograde Admin-istration of Blood Cardioplegia is a safe and simple procedure, but it seems that the routine use of this method cannot improve the patient early outcome significantly in patients underwent primary CABG with non-complex coronary lesion with an aortic cross clamping less than 40 minutes. It is clear that for achieving the definitive results, we need to conduct more studies with more patients. We believe that the combination of retrograde and antegrade route of administration of cardioplegia will be useful for high risk patients including left main or complex coronary lesion, patients with LV dysfunction or concomitant valve procedure and all cases with prolonged ischemic time.

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