ORIGINAL ARTICLE   **Open Access**

Warm blood cardioplegia versus cold crystalloid cardioplegia for coronary artery bypass grafting (CABG) in patients with low ejection fraction

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Abstract

Background: Patients with reduced ejection fraction (EF) undergoing CABG are more likely to develop postoperative morbidity and mortality. It is controversial about which cardioplegia solution, temperature, and method of administration ensure optimal cardiac muscle preservation during CABG surgery.

Aim of the study: The aim of the study was to compare intermittent antegrade warm blood cardioplegia with cold crystalloid cardioplegia during CABG in patients with low EF (30–40%).

Methods: Patients ($n = 100$) undergoing elective isolated on-pump CABG were prospectively randomized into group I ($n = 50$) which received antegrade cold crystalloid cardioplegia and group II ($n = 50$) which received antegrade warm blood cardioplegia. Blood samples were collected immediately and 12 and 24 h postoperatively. CK-MB and cardiac troponin I were measured and compared between the two groups. Other indicators such as use of inotropic support and use of intra-aortic balloon counter pulsation (IABC) were also documented.

Results: Preoperative demographic and clinical variables were matched in both groups. However, postoperative CK-MB and troponin I were higher in group I compared to group II. There was less need for inotropic support and IABC with better postoperative course in group II than in group I.

Conclusion: There was a significant reduction in the release of cardiac enzymes and less need for inotropic support with better postoperative outcome in patients who received antegrade warm blood cardioplegia versus cold crystalloid cardioplegia.

Keywords: Coronary artery bypass grafting, Myocardial protection, Cardioplegia, CK-MB, Troponin T

Introduction

Management of patients with coronary artery disease (CAD) with reduced ejection fraction (EF) remains a challenge, despite the new advances in medical therapy and surgical revascularization (Cleland et al. 2011).

Patients with low EF undergoing coronary artery bypass graft (CABG) (compared with patients with normal left ventricular (LV) function) are usually associated with higher need for inotropic support; intra-aortic balloon pump; longer hours of ventilation, intensive care unit (ICU), and hospital stay; and higher postoperative morbidity and mortality (Flack et al. 2000).

Various techniques for cardioplegia delivery have been developed to optimize myocardial preservation and to decrease ischemia reperfusion injury. The optimal cardioplegia temperature during CABG surgery has been one of the most important aspects of myocardial protection (De Bruyn et al. 2014).

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Blood cardioplegia at physiological temperature will improve the postoperative outcome for better myocardial protection due to the improvement of oxygen availability. Also, blood will improve the oxygen carrying capacity and is less accompanied with hemodilution (Topkara et al. 2005).

Although cold cardioplegia can lower myocardial oxygen consumption and demands, myocardial enzymes may inhibit and delay metabolic and functional cardiac recovery after surgery. Blood cardioplegia will inhibit proteins responsible for ischemia reperfusion-induced apoptosis than crystalloid cardioplegia (Jacob et al. 2008).

Aim of the study

The aim of this study was to compare antegrade warm blood cardioplegia with cold crystalloid cardioplegia during CABG in patients with EF (30–40%) regarding postoperative cardiac enzyme level, postoperative left ventricular ejection fraction, dose of inotropic support, period of the mechanical ventilation, intensive care unit stay, and patient survival.

Patients and methods

This interventional randomized prospective study was conducted on 100 adult patients subjected to elective isolated CABG with low ejection fraction (30–40%) from January to July 2019 in a cardiothoracic surgery operation unit, Ain Shams University hospitals. The study protocol was approved by the "research and ethics committee" of Anesthesia, Intensive Care and Pain Management Department, Ain Shams University. Informed consent was obtained from the patients before enrolling in the study.

All patients underwent preoperative assessment by taking a history of symptoms of ischemic heart disease (IHD) and its risk factors such as hypertension (HTN), diabetes mellitus (DM), and dyslipidemia, routine laboratory investigations plus cardiac enzymes 1 day before the surgery, chest X-ray, and echocardiography.

Patients with cerebrovascular disease and renal failure, single-vessel coronary disease, emergency and redo operation, and other co-existent valve surgeries were excluded from the study.

Anesthesia techniques were standardized in all patients: standard monitoring of pulse oximetry, invasive arterial blood pressure measurement, electrocardiogram (leads II and V5), automatic ST segment orientation analysis, central venous pressure (CVP), end-tidal capnography, and monitoring of pharyngeal temperature and urine output.

Balanced smooth induction of anesthesia with fentanyl 2–5 µg/kg, propofol 1–2 mg/kg, pancuronium 0.1 mg/kg, and inhaled isoflurane 0.5–1% was administered; patients were mechanically ventilated to maintain $EtCO_2$ between 30 and 35 mmHg. Serial blood gas and serum electrolyte analyses were performed.

Patients (n = 100) were classified into two equal groups by computer-generated random variety list.

Group I (intermittent antegrade cold crystalloid cardioplegia): After clamping of the aorta, 10 ml / kg of antegrade crystalloid cardioplegia was administered at (4 ° C).

A second or third shot of crystalloid cardioplegia was given every 15-20 min, with half of the initial dose (5 ml/kg) of the first dose (each 1 liter Ringer solution contained potassium chloride 30-40 mmol/l, xylocaine 100 mg and 1 gram Mg sulfate).
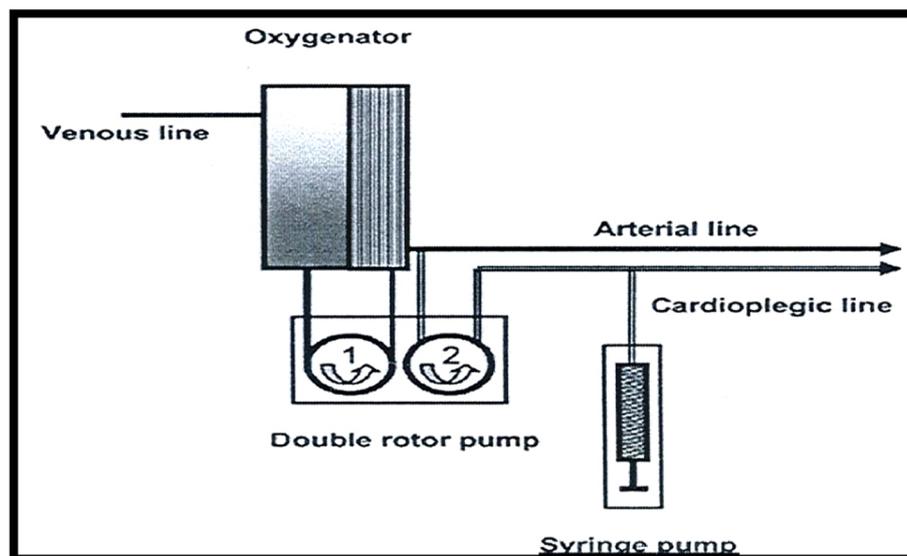

Fig. 1 Method of delivery of warm blood cardioplegia

Table 1 Preoperative data

	Group I (no. = 50)	Group II (no. = 50)	*p* value	Significance
Age (years)				
Mean ± SD	56.5 ± 8.7	57.14 ± 9.6	0.727	NS
Sex				
Males	24 (48%)	25 (50.0%)	0.841	NS
Females	26 (52%)	25 (50.0%)		
Weight (kg)				
Mean ± SD	72.5 ± 2.3	71.8 ± 1.8	0.093	NS
Body surface area (m^2)				
Mean ± SD	1.92 ± 0.6	1.83 ± 0.87	0.548	NS
Diabetes	20 (40%)	23 (46.0%)	0.544	NS
HTN	19 (38%)	20 (40%)	0.837	NS
Smoking	22 (44%)	21 (42%)	0.839	NS
Ejection fraction (%) (mean ± SD)	30.9 ± 0.8	31.1 ± 0.9	0.243	NS
Troponin I levels (ng/ml) (mean ± SD)	0.09 ± 0.68	0.03 ± 0.29	0.718	NS
CK-MB level (IU/l) (mean ± SD)	1.45 ± 1.31	1.26 ± 0.99	0.776	NS

NS not significant (p value ≥ 0.05), *SD* standard deviation, *kg* kilogram, *m^2* square meter

Group II (intermittent antegrade warm blood cardioplegia) (fig. 1): warm (37°C) blood cardioplegia was given after aortic cross clamping.

Rotor no. 1 is an arterial pump that implements the entire bypass flow.

Rotor no. 2 is the cardioplegia pump that redirects the blood component of the warm blood cardioplegic solution in the rate of 300 ml/min pump flow.

The syringe pump contains 50 ml Ringer's solution formed of 30 mEq K chloride, 1 g Mg sulfate, and 100 mg xylocaine; a dose of 30 ml was injected over a period of 3 min.

Another dose was delivered every 30 min in an interrupted manner for 1 min. Vein graft infusion with warm blood cardioplegia was improving the distribution of the solution beyond coronary stenosis. Hot shot (without potassium) was given for 1–3 min before the removal of aortic cross clamp.

Total bypass time, aortic cross clamp time, average distal anastomoses, use of inotropic support (when the systolic blood pressure is lower than 90 mm Hg or MAP is lower than 60 mm Hg with altered tissue perfusion), and the use of intra-aortic balloon pump (when there is no response in spite of adrenaline support usage in the presence of myocardial ischemia) were recorded in both groups (Reynolds and Hochman 2008).

Serial blood samples for CK-MB and troponin I which were obtained postoperatively at 0, 12, and 24 h were analyzed.

Postoperative courses such as duration of ventilation, ICU, and hospital stay were recorded.

Echocardiography was performed before the surgery and was followed up for 14 h, 1 week, and 3 months postoperatively, and mortality was recorded within 30 days postoperatively.

Outcomes of the study

Our primary outcome is the postoperative cardiac enzyme level (troponin I); secondary outcomes include postoperative left ventricular ejection fraction, CK-MB

Table 2 Intraoperative data

	Group I (no. = 50)	Group II (no. = 50)	*p* value	Significance
Total bypass (min) (mean ± SD)	85.3 ± 13.6	90.1 ± 12.5	0.069	NS
Cross clamp (min) (mean ± SD)	56.7 ± 19.3	58.2 ± 17.6	0.686	NS
Average number of distal anastomoses (mean ± SD)	3.2 ± 0.8	3.0 ± 0.5	0.137	NS
Use of inotropic support [number of patients (%)]	42 (84%)	13 (26%)	< 0.001	HS
Use of IAB [no. (%)]	8b (16%)	1 (2%)	0.014	S

HS highly significant (p value < 0.001), *S* significant (p value < 0.05), *NS* not significant (p value ≥ 0.05), *min* minutes, *SD* standard deviation, *IAB* intra-aortic balloon

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Table 3 Postoperative troponin I level (ng/ml)

	Group I (no. = 50) Mean ± SD	Group II (no. = 50) Mean ± SD	*p* value	Significance
Immediate postoperative level (ng/ml)	1.76 ± 0.72	1.02 ± 0.20	< 0.001	HS
12 h postoperative level (ng/ml)	6.36 ± 1.55	3.21 ± 0.48	< 0.001	HS
24 h postoperative level (ng/ml)	8.61 ± 1.26	2.15 ± 0.45	< 0.001	HS

HS highly significant (*p* value < 0.001), *SD* standard deviation, *ng/ml* nanograms/milliliter

level, use of inotropic support, period of the mechanical ventilation, intensive care unit stay, and patient survival.

Statistical analysis

Data were collected, reviewed, coded, and entered into the Statistical Package for Social Sciences (IBM SPSS), version 23. Quantitative data were presented as mean, standard deviations, and ranges when their distribution was found to be parametric. Also, qualitative variables were presented as number and percentages. The comparison between two groups regarding qualitative data was done by using *chi-square test* and *Fisher's exact test* instead of chi-square test when the expected count in any cell was found to be less than 5. Qualitative variables are also presented as numbers and percentages. Two groups were compared in qualitative data using chi-square test and Fisher's exact test instead of chi-square test when the expected number in a cell was less than 5. Two independent groups were compared with quantitative data and parametric distribution using the independent *t* test, while the non-parametric distribution used the Mann-Whitney test.

Sample size estimation

A difference was shown in troponin I levels with a confidence interval at 95% and the acceptable margin of error at 5%. Therefore, the *p* value was considered significant at < 0.05; we needed a sample size of 50 patients per group for the comparison of the effect of warm blood cardioplegia versus cold crystalloid cardioplegia for coronary artery bypass grafting in patients with low ejection fraction.

Results

There was no statistically significant difference between the two groups in terms of preoperative data (Table 1).

There was no statistically significant difference between the two groups as regards bypass time, cross clamping time, and numbers of distal anastomosis. However, there was a statistically highly significant difference between the two groups with regard to the use of inotropic support (42 patients in group I versus 13 patients in group II) (other patients did not need inotropic support) and the use of the intra-aortic balloon (8 patients in group I versus one patient in group II) as shown in Table 2.

Postoperative troponin I level

There was a statistically significant difference in all samples (immediate postoperative and 12 h and 24 h postoperative between the two groups). The release of troponin I was significantly lower in the warm
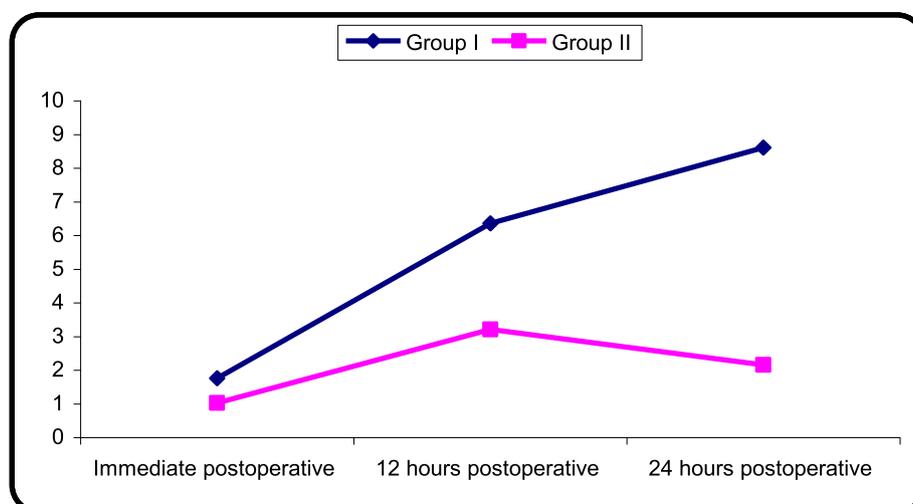

Fig. 2 Postoperative troponin I level (ng/ml)

Table 4 Postoperative CK-MB level (IU/l)

	Group I (no. = 50) Mean ± SD	Group II (no. = 50) Mean ± SD	*p* value	Significance
Immediate postoperative level (IU/l)	25.8 ± 27.3	15.6 ± 12.6	0.018	S
12 hours postoperative level (IU/l)	16.8 ± 4.2	10.5 ± 2.3	< 0.001	HS
24 hours postoperative level (IU/l)	12.8 ± 5.3	7.5 ± 2.6	< 0.001	HS

HS highly significant (*p* value < 0.001), *S* significant (*p* value < 0.05), *SD* standard deviation, *IU/l* international units/liter

cardioplegia group (group II) as shown in Table 3 and Fig. 2.

As regards postoperative CK-MB level, there was a statistically significant difference in all samples (immediate postoperative and 12 h and 24 h postoperative between the two groups). CK-MB release was significantly lower in the warm cardioplegia group (group II) as shown in Table 4 and Fig. 3.

Postoperative data
There was a statistically significant difference between the two groups, as regards the duration of mechanical ventilation and ICU stay as shown in Table 5.

Mechanical ventilation and ICU stay time was significantly lower in warm cardioplegia.

There was a statistically significant difference between the two groups as regards the postoperative left ventricular ejection fraction at 14 h, 1 week, and 3 months postoperatively as shown in Table 6.

Mortality
Mortality was 5 patients in the cold crystalloid cardioplegia group and 1 patient in the warm blood cardioplegia group; this difference is not statistically significant (*p* value = 0.20) [*p* value ≥ 0.05(not significant)].

Discussion
Despite threatening prognosis of advanced ischemic cardiomyopathy, coronary artery bypass grafting remains controversial due to concerns about operational risks and lack of functional benefits and survival (Elefteriades et al. 1993).

Patients with low ejection fraction (EF) are at greater risk for postoperative complications and mortality than patients with high EF. However, the results improve over time and outperform historical data. There, CABG remains a viable option in selected low-EF patients (Robinson et al. 1995).

Postoperative outcome will be improved in these types of patients with low EF if they received adequate and optimum cardioplegia solution for myocardial preservation especially warm blood cardioplegia (Guru et al. 2006).

CABG has been shown to be superior to drug therapy in low-EF patients alone, indicating significant clinical improvement and long survival (Robinson et al. 1995).

Guru et al. (Guru et al. 2006) demonstrated a data analysis of 4316 patients who underwent cardiac surgery with blood or crystalloid cardioplegia. In their analysis, compared to crystalloid cardioplegia, blood cardioplegia provided superior myocardium protection in terms of lower incidence of low-output syndrome
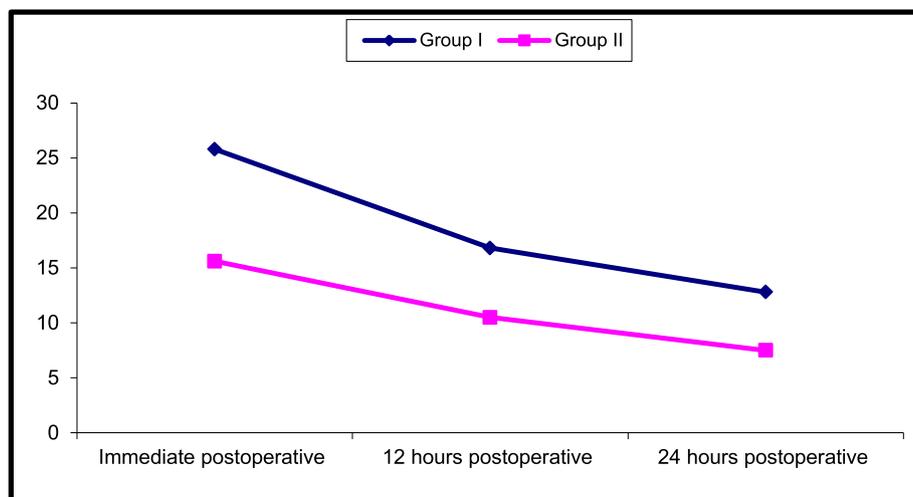

Fig. 3 Postoperative CK-MB level (IU/l)

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Table 5 Postoperative data

	Group I (no. = 50)	Group II (no. = 50)	*p* value	Significance
Mechanical ventilation (h) (mean ± SD)	10.35 ± 5.67	6.78 ± 3.21	< 0.001	HS
ICU stay (days) (mean ± SD)	3.5 ± 1.85	2.1 ± 1.2	< 0.001	HS
Reopening	5 (10%)	3 (6%)	0.712	NS

HS highly significant (*p* value < 0.001), *NS* not significant (*p* value ≥ 0.05), *h* hour, *ICU* intensive care unit, *SD* standard deviation

and reduced release of CK-MB, although deaths, myocardial infarction, and low cardiac output syndrome were similar.

Fiore et al. (Fiore et al. 1998), in a single-center study, reported that intermittent warm blood cardioplegia was a more effective means of protecting the myocardium than intermittent cold blood cardioplegia in 52 patients with elective CABG patients as measured by the reduced CK-MB enzyme release after surgery ($p < 0.04$), improved left ventricular function ($p < 0.05$), and reduced need for inotropic support ($p < 0.05$), although there were small statistical differences, as reported.

The goal of protecting the myocardium during treatment surgery was to maintain myocardial function while providing a bloodless and motionless surgical field (Fiore et al. 1998).

Hypothermia reduces myocardial oxygen demand but retards postoperative metabolic recovery and myocardial function and shifting of oxy-HB dissociation curve to the left leading to reduced oxygen availability. Blood cardioplegia allows aerobic cardiac metabolism during aortic cross clamp with minimal lactate production and less metabolic acidosis (Fiore et al. 1998).

In this study, we compared the two methods of cardioplegia: intermittent antegrade crystalloid cold cardioplegia or intermittent warm blood cardioplegia.

The study was conducted on 100 patients who underwent elective isolated coronary artery bypass grafting.

Patients were divided into two groups, with the first group (I) ($n = 50$) receiving intermittent antegrade cold crystalloid cardioplegia and the second group (II) ($n = 50$) receiving intermittent antegrade warm blood cardioplegia.

The parameters used to evaluate the two methods of myocardial preservation were the inotropic support, the use of IABC, CK-MB, and cardiac troponin as markers for myocardial injury, the ICU stay and period of mechanical ventilation, the postoperative LV EF, and the mortality rate to reflect the clinical outcome.

In our study, only one antegrade method was used to provide cold and warm cardioplegia.

Balba et al. (Balba et al. 2014) showed that the combined antegrade and retrograde cardioplegia had the same clinical outcome as antegrade cardioplegia alone.

But Dar et al. (Dar 2005) found that the troponin and CK-MB levels were significantly lower with better myocardial protection in antegrade combined with retrograde warm blood cardioplegia than antegrade cold crystalloid and antegrade warm blood cardioplegia. The combined routes of administration allow better outcome and homogenous myocardial preservation, as myocardial areas after complete occlusion are poorly protected by the antegrade route alone.

Because poor LV function is a major predictor for higher operative mortality, we studied the effect of cardioplegia on outcome and survival on patients with low EF% (40–30%) undergoing CABG.

In this study, we experienced 42 cases (84%) who needed inotropic support in cold crystalloid group versus 13 cases (26%) in warm blood group which was statistically highly significant.

Mourad et al. (Cleland et al. 2011) reported that 25 cases (25%) require inotropic support longer than 24 h and 18 cases (72%) of these patients were in the cold crystalloid group which was statistically significant.

There is a significant decrease in the release of cardiac enzymes in patients who also received antegrade warm blood cardioplegia with less myocardial cell injuries than cold cardioplegia. The same results were found in a meta-analysis of 41 randomized controlled trials (RCTs) by Fan and Coworkers (Fan et al. 2010) in 2010. They reported that CK-MB and troponin I levels in the warm cardioplegia group decreased significantly compared to the cold cardioplegia group in the postoperative period.

Table 6 Postoperative left ventricular ejection fraction (%)

	Group I (no. = 50)	Group II (no. = 50)	*p* value	Significance
	Mean ± SD (%)	Mean ± SD (%)		
14 h postoperative	30.0 ± 7.0	35.0 ± 5.0	< 0.001	HS
1 week postoperative	37.5 ± 5.0	44.6 ± 6.0	< 0.001	HS
3 months postoperative	45.0 ± 6.0	53.0 ± 4.0	< 0.001	HS

HS highly significant (*p* value < 0.001), *SD* standard deviation

Mechanical ventilation and ICU stay time was significantly low with better economic view and lower complications of mechanical ventilation in warm cardioplegia type.

Although Murad et al. reported that there was no significant difference between the two groups regarding LV function following echocardiography, we noted, however, that there was a highly significant difference between the two groups in terms of postoperative LV EF.

Conclusion

This study shows that there is a significant decrease in cardiac enzyme release and also a significant decrease in inotropic support usage with better postoperative outcome, less need of mechanical ventilation postoperatively, and less ICU stay in patients with low ejection fraction who received antegrade warm blood cardioplegia than those who received cold crystalloid cardioplegia.

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