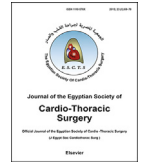


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Original article

# Myocardial protection during CABG: Warm blood versus cold crystalloid cardioplegia, is there any difference?

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## Abstract

**Background:** Up till now there is lack of consensus to the optimal method for cardioplegia delivery in coronary artery bypass graft (CABG) patients. Various strategies have been developed to minimize ischemic-reperfusion injury.

The aim of this study was to compare cold crystalloid cardioplegia and warm blood cardioplegia in patients undergoing CABG. **Methods:** Patients (n = 100) undergoing CABG were prospectively randomized into group 1 (n = 50) which received antegrade cold crystalloid cardioplegia, group 2 (n = 50) which received antegrade warm blood cardioplegia. Blood samples were collected immediately, 12, and 24 h postoperatively and CK, CKMB, and Cardiac Troponin I were measured and compared between the two groups which were the indicator of myocardial cell injury (the primary end point of this study). Other indicators such as spontaneous defibrillation, use of intra-aortic balloon counter pulsation (IABC), and use of inotropic support were also documented.

**Results:** Preoperative demographic and clinical variables were matched in both groups. However, intraoperatively, the use of inotropic support was significantly higher in Group I compared to Group II (P = 0.032). Postoperative CK, CKMB and Troponin I were significantly higher in group (I) compared to group (II).

**Conclusion:** A significant reduction in the release of cardiac enzymes in patients who received antegrade warm blood cardioplegia suggests better myocardial protection compared to cold crystalloid cardioplegia.

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**Keywords:** Coronary artery bypass; Creatine kinase (CK); Troponin I; Ischemia-reperfusion injury

## 1. Introduction

The use of cardiopulmonary bypass (CPB), cardioplegic arrest, and subsequent reperfusion of the heart causes a systemic inflammatory response and ischemia-reperfusion injury, which are responsible for significant postoperative morbidity [1].

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Cardioplegic arrest of the heart in diastole is induced and maintained by injecting a potassium rich fluid into the coronary arteries, reducing the heart's oxygen consumption by about 90%, when the fluid is administered at physiological temperature [2].

The medium into which the potassium is mixed can be either blood or crystalloid solution. Both of these can be administered cold (4 °C–10 °C), which can further reduce oxygen consumption in the arrested heart [3,4].

Cold crystalloid solutions were introduced in the early 1950s and continued to be used widely until the 1980s when cold blood-based potassium solutions were introduced. The latter were shown to improve surrogate endpoints such as biomarkers of myocardial damage (for example CK-MB) [4] but not clinical outcomes, so many surgeons continued to use crystalloid solutions.

The adoption of warm blood cardioplegia (>28 °C) during the 1990s was based on trials that showed improved cardiac index and less enzyme release after surgery.

Blood cardioplegia administered at the physiological temperature may protect the heart during CABG and reduce adverse postoperative events. This is because blood (as opposed to crystalloid solutions) as a medium for cardioplegia delivery has greater oxygen carrying capacity and is less associated with hemodilution and therefore more closely resembles normal physiology. A higher temperature also improves oxygen availability in blood cardioplegia. Blood cardioplegia is superior to crystalloid cardioplegia in inhibiting proteins responsible for ischemia-reperfusion-induced apoptosis [5].

Currently there is no consensus as to the optimal method for cardioplegia delivery to minimize myocardial injury in CABG patients.

Various strategies have been developed to try and minimize ischemia-reperfusion injury, including the use of mini-CPB, 'ischemic pre-conditioning' of the heart to make it more resistant to injury and optimizing the method of cardioplegic arrest, which is the focus of this study.

## 2. Patients and methods

The study was conducted on 100 adult patients who underwent isolated CABG in the department of cardiothoracic surgery in Ain Shams University during 2014 & 2015.

Patients were divided two groups:

- Group I: antegrade cold crystalloid cardioplegia with topical cooling (n = 50).
- Group II: antegrade warm blood cardioplegia (n = 50).

### 2.1. Exclusion criteria

- I. Patient with single vessel disease.
- II. Patients in congestive heart failure.
- III. Coexistent condition with significant mortality.
- IV. Emergency & Redo operations.
- V. Other co-existent valve lesion.

All patients were subjected to

#### A) Preoperative assessment:

1. Thorough history taking with emphasis on symptoms of ischemic heart disease (IHD), carotid artery disease, peripheral arterial disease, risk factors for IHD (smoking, DM, hypertension ... etc)
2. Routine preoperative laboratory investigations with stress on Troponin I & CK MB the day before surgery.
3. Chest x-ray for all patients.
4. Echocardiography for all patients on regional wall motion abnormalities (RWMA), Ejection Fraction (EF), and any other pathology.

**B) Intraoperative:**

The patients were monitored by:

1. ECG.
2. Body temperature.
3. Saturation using pulsed oximetry.
4. Invasive blood pressure monitoring.
5. Arterial blood gases.
6. CVP measurement using central venous line catheter.
7. The need for inotropic drugs or IABC after CABG.
8. Cardiac bypass time.
9. Aortic cross clamp time.
10. Number of coronary artery grafts.

**2.2. Postoperative**

1. Troponin I & CKMB immediately, 12 & 24 h post-operative.
2. Period of ICU stay.
3. Period of stay on ventilator.
4. The dosage & period of inotropes if present.
5. Incidence of renal dysfunction assessed by kidney function tests (elevated serum creatinine more than 2 mg/dl or double the baseline preoperative value).
6. Incidence of myocardial infarction.
7. Postoperative ECHO for RWMA or pericardial effusion or any other abnormalities.
8. Outpatient clinical follow up and echocardiography 3 months after surgery for all patients and any problem was recorded.

**3. Results**

The study was conducted on 100 consecutive patients who underwent isolated elective CABG in Cardiothoracic Surgery Department in Ain shams University Hospitals during 2014 & 2015.

All data were entered in computerized database, and analyzed with SPSS program version 10.0. Results were statistically represented in the term of mean and standard deviation. Continuous data (of different groups) were compared with paired t-test and categorical data by Pearson's Chi-square test. A p-value <0.05 was considered statistically significant.

**3.1. Preoperative data**

There was no statistical difference between the two groups as regards their preoperative characteristics. And [Table 1](#) shows the preoperative characteristic of the study groups.

**3.2. Intraoperative data**

There was no statistically significant difference between the two groups as regards bypass and cross clamp times. However, there was a statistically significant difference between the two groups as regards spontaneous defibrillation (8 patients in Group I versus 46 patients in Group II) and the use of inotropic support (17patients in Group I versus 8patients in Group II) ([Table 2](#)).

**3.3. ICU data**

[Table 3](#) shows ICU events in both groups. It showed that the postoperative blood transfusion was significantly higher in Group II during the first 24 h. However, there was no statistical significance as regards reopening for

Table 1  
Preoperative characteristics.

Demographic data	Group I N = 50	Group II N = 50	P value	Significance
Age (years) Mean $\pm$ SD	57.4 $\pm$ 9.2	57.9 $\pm$ 9.2	0.66	NS
Sex (% of female)	5 (10%)	8 (16%)	0.32	NS
Weight (kg) Mean $\pm$ SD	73.4 $\pm$ 1.6	70.6 $\pm$ 1.4	0.16	NS
Body surface area Mean $\pm$ SD	1.91 $\pm$ 0.5	1.89 $\pm$ 2.2	0.855	NS
Diabetes	19 (38%)	18 (36%)	0.8	NS
Hypertension	20 (40%)	24 (48%)	0.25	NS
Smoking	22 (44%)	15 (30%)	0.45	NS
CVA	0	0	1	NS
Mean EF (%) Mean $\pm$ SD	45.8 $\pm$ 8.6	46.5 $\pm$ 7.78	0.71	NS
Average NYHA class Mean $\pm$ SD	2.1 $\pm$ 0.6	1.9 $\pm$ .54	0.14	NS
LMCA disease (>50%)	5 (10%)	3 (6%)	0.72	NS

bleeding. Also, there was no significant difference between 2 groups as regards duration of mechanical ventilation and ICU stay.

### 3.4. Cardiac enzymes after surgery

Serum samples for cardiac enzymes (CK, CK-MB, and Troponin I) were taken immediately postoperatively, 12, and 24 h after arrival to ICU.

As regards CK, and CK-MB enzymes, there was a statistically significant difference in the 3rd sample (after 24 h) between the two groups, with the lower level in Group II. However, Troponin I release was significantly lower in warm cardioplegia Group II (Tables 4–6).

### 3.5. Postoperative and discharge data

There was no statistically significant difference between the two groups as regards postoperative complications.

At the time of discharge, all patients had echocardiography. There was no statistically significant difference between the two groups as regards LV function.

### 3.6. Follow up data

Clinical assessment and follow up echocardiography was done for study patients 3 months after surgery and there was no statistically significant difference between the two groups.

Table 2  
Intraoperative data.

Variable	Group I	Group II	P value	Significance
Total bypass (min).	87 $\pm$ 14	94 $\pm$ 11	0.301	NS
Cross clamp (min).	58 $\pm$ 23	61 $\pm$ 15	0.433	NS
Average distal anastomoses.	3.4 $\pm$ 0.9	3.1 $\pm$ 0.4	0.244	NS
Spontaneous defibrillation.	8 (16%)	46 (92%)	<001	Highly significant
Use of inotropic support.	17 (34%)	8 (16%)	0.032	Significant
Use of IABC.	1 (2%)	1 (2%)	1	NS
Intraop. blood transfusion.	3 (6%)	1 (2%)	0.15	NS

NS = nonsignificant.

Table 3  
ICU events.

Variable	Group I	Group II	P value	Significance
Perioperative MI.	0	0	1	NS
Blood transfusion.	18(36%)	40(80%)	<0.001	HS
Reopening.	4(8%)	3(6%)	0.51	NS
Mechanical ventilation (h).	15.53 ± 7.2	13.1 ± 6.89	0.12	NS
ICU stay (days).	2.48 ± 0.65	2.1 ± 0.47	0.053	NS

NS = nonsignificant, HS = highly significant.

#### 4. Discussion

The aim of myocardial protection during heart surgery was to preserve myocardial function while providing a bloodless and motionless operating field. In the early stage, myocardial protection was obtained by decreasing myocardial oxygen demand as a consequence of hypothermia [6]. Although intermittent cold cardioplegia perfusion is associated with excellent clinical outcomes in cardiac surgery, this standard technique results in myocardial hypothermia, ischaemia and a delay in the recovery of postoperative myocardial metabolism and function [7].

In addition, it was demonstrated that with electromechanical arrest alone, one could reduce the oxygen requirements of the heart by nearly 90%, with only a slight further decrease attributable to lowering myocardial temperature to 11 °C [8]. Based on these considerations, warm blood cardioplegia perfusion during heart surgery procedure was clinically applied since 1980 [9]. It was once believed that the use of warm blood cardioplegia could improve metabolic and functional recovery, and this technique has been adopted by many cardiac surgeons since the early 1990s [10]. Potential advantages of this technique, as described by Calafiore et al. were minimal dilution of the patient and economic consideration as the method is simple and doesn't require expensive equipment such as heat exchanger [11].

Blood cardioplegia facilitates aerobic myocardial metabolism during cross clamp period and reduces anaerobic lactate production [12]. Intermittent antegrade warm blood cardioplegia preserves systolic function and improves both systolic and diastolic chronotropic response [13].

However, after being used for more than 30 years, there is still much controversy regarding whether warm cardioplegia is superior to cold [6].

In this study we compared the two modalities of cardioplegia either antegrade cold crystalloid or warm blood cardioplegia. The study was conducted on 100 consecutive patients underwent elective isolated CABG procedure. The patients were classified into two groups. The first group I (n = 50) received intermittent antegrade cold crystalloid cardioplegia, and the second group II (n = 50) received intermittent antegrade warm blood cardioplegia. We decided to use CK, CK-MB, and cardiac Troponin I as markers for myocardial damage due to their specificity and the fact that they are far more reliable than postoperative ECG changes that may be blurred by new onset conduction disturbances, which is not uncommon in the early postoperative period.

The two groups were comparable as regards their demographic characters with the mean age in Group I was 57.4 years versus 57.9 years in Group II. The two groups were also comparable as regards the sex distribution, the body mass index, and other comorbidities.

Jacquet et al. [14] reported an average age 65.2 ± 8.5 in cold crystalloid group and 64.5 ± 9.6 in warm blood group, with female percentage of 27.5% in contrast to our study which had the female percentage of 13%. A recent study by Zeriuoh et al. [15] reported a 35.6% of patients more than 70 year of age with 20.8% female ratio.

The incidence of hypertension and diabetes in this study was 44% and 37% respectively. The incidence of hypertension in Jacquet et al. [14] study was 50.5% which was slightly higher than ours. But in Sirvinskas study there was a percentage of 42.3 of hypertension [16] which was comparable to this study. There was a very high percentage

Table 4  
Postoperative CK level (IU).

Enzyme	Group I	Group II	P value	Significance
Immediate postop.	912 ± 472	831 ± 495	0.63	NS
12 h postop.	863.9 ± 449	639.9 ± 344	0.28	NS
24 h postop.	769.3 ± 360	485.2 ± 247	0.002	HS

Table 5  
Postoperative CKMB level (IU).

Enzyme	Group I	Group II	P value	Significance
Immediate postop.	22.8 ± 37.3	14.4 ± 28.8	0.66	NS
12 h postop.	15.3 ± 3.3	13.9 ± 2.15	0.091	NS
24 h postop.	13.93 ± 5.2	7.21 ± 3.1	0.0013	HS

NS = nonsignificant, HS = highly significant.

of hypertension in Zeriouh et al. study groups which was 85% [15]. The incidence of diabetes in Zeriouh study was 35.3% which was comparable to our study [15].

Poor LV function has been shown previously to be an independent predictor of higher operative mortality [17]. In our study we excluded patients with poor ejection fraction, and the average EF for the patients was 46.16% which is similar to group I in Zikri et al. [23]. Also there was no statistically significant difference between the two groups in the study with the mean EF in Group I was 45.8% versus 45.6% in Group II. However, Elwatidy et al. reported 5.5% of their patients to have EF less than 30% [18]. The incidence of poor LV function (EF < 35%) in Calafiore study was 16.2% [11].

The left main coronary artery is an important system, and its stenosis has a very considerable impact on survival. Coronary Artery Surgery Study (CASS) Registry showed that the 5 year survival rate in asymptomatic patients with left main coronary artery disease (LMCAD) was 57%, and 58% in symptomatic patients [19].

The incidence of significant LMCAD (>50% stenosis) in our study was 8%. The percentage was higher in patients in our study group I but was statistically comparable to the group II.

Most of the patients in our study had triple vessel disease. Patients with severe coronary artery disease (stenosis >80%) represented 70% of our patients. Comparable to our study was the Calafiore study who reported an incidence of 7% of LMCAD [11].

The average bypass time and cross clamp time in our study was 90.5 ± 12.5 min, and 59.5 ± 19 min respectively corresponding to average three distal anastomoses. Calafiore et al. reported 67.2 ± 21.3 to 76.3 ± 27.5 min average bypass time, and 45.2 ± 16.3 to 44.8 ± 15.2 min average cross clamp time [11]. Zeriouh et al. reported 77.96 ± 25.20 to 82.93 ± 32.25 min average bypass time for elective CABG, and 39.92 ± 12.65 to 43.96 ± 15.85 min average cross clamp time [15].

In this study; the parameters used to evaluate the two methods of myocardial preservation were spontaneous defibrillation which indicated the myocardial recovery after declamping, the CK, CKMB, and Troponin I to assess ischemic myocardial injury, the inotropic support, the use of IABC, the ICU stay, the mechanical ventilation, and the mortality rate to reflect the clinical outcome in relation to myocardial protection.

In our study the incidence of spontaneous defibrillation was 54%. There was statistically significant difference between the two groups with incidence of 92% in warm blood group II compared to 16% in cold crystalloid group I. Jacquet et al. reported 96.2% spontaneous defibrillation of intermittent warm blood cardioplegia versus 83.6% in cold crystalloid group [14]. Elwatidy et al. reported 95.7% spontaneous defibrillation in warm blood group compared to 2.5% in cold crystalloid group [18]. The higher incidence of spontaneous defibrillation in our study might be due to the application of hot shot of warm blood before declamping in many of the patients in group II.

In this study we experienced 25 cases (25%) who needed prolonged inotropic support (>24 h), 72% (18) of those patients were in cold crystalloid group I which was statistically significant. The use of IABC was 2% in overall study and was comparable between the two groups.

The serum total CK, CKMB, and cTn were serially measured immediately postoperative, at 12, and 24 h post arrival to ICU. As regards CK, and CKMB, there was no statistical difference between the two groups in the first two sets of measurements (immediate and 12 h), but there was a highly significant decrease in their release after 24 h in

Table 6  
Postoperative Troponin I level (µg/L).

Enzyme	Group I	Group II	P value	Significance
Immediate postop.	1.76 ± 0.32	1.26 ± 0.20	<0.05	S
12 h postop.	6.20 ± 1.15	5.21 ± 0.48	<0.01	HS
24 h postop.	6.81 ± 1.26	4.15 ± 0.57	<0.01	HS

S = significant, HS = highly significant.

warm blood cardioplegia group II in comparison to group I. In contrast to CK and CKMB measures, the decrease of myocardial release of cTn was highly significant immediately postoperative, 12, and 24 h after arrival to ICU. Elwatidy et al. [18] reported significant lower release of CK and CKMB in tepid blood group compared to cold crystalloid group. Franke et al. [20] study showed significant lower CKMB and cTn release in warm blood group. Guru and coworkers [21] in 2006 performed a meta-analysis of 34 randomized clinical trials (RCT) and reported that there was a significant increase in CK-MB release with cold crystalloid cardioplegia in comparison to crystalloid cardioplegia.

Fan and coworkers [6] in 2010 performed a meta-analysis of 41 randomized controlled trials (RCTs) comparing cold and warm cardioplegia for myocardial protection in patients undergoing heart surgery. They reported that the concentrations of both cTn and CK-MB were significantly reduced in warm group after surgery as compared with the cold group.

Routine postoperative assessment of EF was done to all patients between the 4th and 6th postoperative day. The average postoperative EF was  $49.23 \pm 9.43\%$  in cold crystalloid group I, and  $45.83 \pm 9.68\%$  in group II. The two groups were comparable in their postoperative LV function.

Follow up echocardiography was done 3 months postoperatively. There was no significant difference between the two groups as regards their follow LV function. The average EF after 3 months was  $54.3 \pm 5.6\%$  in patients who received cold crystalloid cardioplegia, and was  $51.2 \pm 7.0\%$  in patients who received warm blood cardioplegia.

The mortality rate in our study was 1%, with 1 patient died in warm blood group II. This mortality rate was statistically insignificant.

The results in this series contradicts those of De Bruyn and his colleagues were they found no benefit of using warm blood cardioplegia over crystalloid cardioplegia [22]. However, our results in this study confirmed the results of the large meta-analysis study of Guru and coworkers [21], and showed that there was less cardiac enzymes release after the application of warm blood cardioplegia for myocardial protection in patients undergoing CABG as compared to cold crystalloid cardioplegia. That indicates less myocardial cell injury associated with warm blood cardioplegia. Accordingly, this study showed that there is no difference in the Egyptian population from the western one in this concern.

In this study, only antegrade method of delivery of cardioplegia was done. Previous studies done also in Egypt showed that cardioplegia delivery method had no effect on the primary end point of having a better clinical outcome in the form of a significant difference in the post-operative mortality, complication rate or LV functions [23,24]. Hence, further studies with a larger number of patients are recommended to combine the comparisons of the technique of delivery (antegrade or retrograde), type (blood or crystalloid) and temperature (cold or warm) of cardioplegia in terms of mortality, postoperative complications and LV functions as primary end points.

## Conflict of interest

No conflict of interest to declare.

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