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Original Article

The effect of cold crystalloid versus warm blood cardioplegia on the myocardium during coronary artery bypass grafting

Elsayed A Fayad[1], Wesam F Aly Eddin[2], Mohamed A Amr[1]

[1] Department of Cardiothoracic Surgery, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

[2] Department of Anesthesia, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

Abstract

Background: The optimal cardioplegic solution is still debated. The objective of this study was to compare the effect of cold crystalloid versus warm blood cardioplegia on the myocardial injury during coronary artery bypass grafting.

Methods: The study included 34 consecutive patients who underwent elective primary on-pump isolated coronary artery bypass grafting from 2016 to 2019. We randomly assigned the patients into two groups. Group (ICCC) (n= 17) received intermittent antegrade cold crystalloid cardioplegia and Group (IWBC) (n= 17) received intermittent antegrade warm blood cardioplegia.

Results: There was no difference in the preoperative and operative variables between groups. The time taken by the heart to regain normal sinus rhythm was significantly longer in the cold crystalloid group (7.06 ± 1.8 vs. 2.17 ± 0.8 minutes, p<0.001) with a higher rate of reperfusion ventricular arrhythmia (35% versus 6%; p=0.03) compared to the warm blood cardioplegia group. Both coronary sinus acid production and lactate level were significantly higher in the warm blood group than in the cold crystalloid group (p< 0.001 and 0.043, respectively). The ischemic ECG changes and the severity of new segmental wall motion abnormalities were non-significantly different between both groups (p= 0.68 and 0.67, respectively). Postoperative CK-MB and cTnI levels in all-time points were not significantly different between groups (p= 0.46 and 0.37, respectively). ICU (2.29 ± 0.77 vs. 2.41 ± 0.87 days, p= 0.68) and hospital stay (9.28 ± 0.76 vs. 9.42 ± 0.88 days, p= 0.62) were non-significantly different between both groups.

Conclusion: Intermittent antegrade cold crystalloid cardioplegia was associated with attenuated myocardial metabolism. However, it was associated with a longer time to regain normal sinus rhythm and more reperfusion ventricular arrhythmias. We did not find differences in the clinical and echocardiographic outcomes and cardiac enzymes between cold crystalloid and warm blood cardioplegia.

KEYWORDS

Cardiac protection; Metabolism; Laboratory; Arrest; Ejection fraction; Motion abnormality

Article History

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Introduction

Despite the improvement of myocardial preservation during cardiac surgery, myocardial damage is inevitable. Cardioplegia is an essential strategy, which provides motionless cardiac surgery and preserves the myocardium. Several cardioplegia additives and techniques have been proposed; however, the optimal cardioplegic solution has not been reached yet [1].

Corresponding author: Elsayed A Fayad sayedfayad_cts@med.suez.edu.eg

Cardioplegia can be achieved either by crystalloid (cold) or blood-based (warm or cold); it can be given continuously or intermittently via antegrade or retrograde routes. Cold crystalloid cardioplegic solutions include the extracellular group as (St Thomas' solution and its modifications) where it contains a high concentration of sodium, calcium, and magnesium and the intracellular group as Custodiol (HTK) [histidine - tryptophan -ketoglutarate] where it consists of a low concentration of sodium and calcium. Both types have a high concentration of potassium [2, 3]. Custodiol cardioplegia is believed to be convenient, simple to deliver, and less time-consuming. Custodial cardioplegia induces cardiac arrest in diastole via hyperpolarization that mimics the natural heart resting state to minimizes metabolic demand and decreasing ATP depletion, thus improving the heart conditions at surgery conclusion. On the contrary, cold cardioplegic solutions induce cardiac arrest by membrane depolarization and have several advantages, including economical cost, while achieving satisfactory clinical results and efficacy in different patients' groups.

Warm heart surgery is achieved through continuous perfusion of blood cardioplegia. During coronary artery grafting (CABG), perfusion is usually interrupted for better visualization during distal coronary anastomosis [4]. Blood cardioplegia provides a more physiological environment for the myocardium; however, it can impair visualization during the construction of coronary anastomoses [1].

Currently, the optimal method for cardioplegia delivery to minimize myocardial injury is unknown. Moreover, there is an ongoing debate about the blood temperature if blood cardioplegia is used; additionally, the optimal delivery media, either blood or crystalloid, is still debated [5]. Consequently, there no standardized practice among surgeons [6, 7]. Meta-analyses were published comparing different cardioplegic solutions [8]; however, the included studies contained heterogeneous populations.

Myocardial injury is more evident in a particular subset of patients, such as those with

Table 1: Preoperative data in both study groups. Continuous data are presented as mean± SD and categorical variables as number and percent.

Variables	ICCC group (n=17)	IWBC group (n=17)	*p* value
Age (Years)	56.0 ± 7.7	54.7 ± 7.4	0.638
Male/Female	11/6	13/4	0.452
Height (cm)	1.763 ± .044	1.774 ± .0385	0.441
Weight (kg)	89.1 ± 7.8	88.1 ± 8.1	0.733
BMI (kg/m^2)	30.7 ± 3.2	30.0 ± 2.9	0.509
ASA (II/III)	9/8	6/11	0.300
Diabetes	9 (52.9%)	11 (64.7%)	0.486
Hypertension	9 (52.9%)	7 (41.2%)	0.492
Diabetic hypertensive	6 (35.3%)	4 (23.5%)	0.452
Smoking	8 (47.1%)	11 (64.7%)	0.300
Number of diseased vessels			
One	2 (11.8%)	2 (11.8%)	0.879
Two	6 (35.3%)	5 (29.4%)	
Three	7 (41.2%)	9 (52.9%)	
Four	2 (11.8%)	1 (5.9%)	
Preoperative wall motion abnormality			
Mild hypokinesia	11 (64.7%)	9 (52.9%)	0.784
Severe hypokinesia	3 (17.6%)	4 (23.5%)	
Preoperative LVEF (%)	52.47 ± 5.23	51.29 ± 5.42	0.525

ASA: American Society of Anesthesiology; ICCC: intermittent cold crystalloid cardioplegia; IWBC: intermittent warm blood cardioplegia; LVEF: left ventricular ejection fraction.

impaired ventricular function. Myocardial injury may manifest clinically as low cardiac output syndrome, arrhythmias, or segmental heart wall motion abnormalities [9]. Several studies have compared warm and cold cardioplegia with no conclusive outcomes. The objective of this study was to compare the effect of cold crystalloid versus warm blood cardioplegia on the myocardial injury during coronary artery bypass grafting.

Patients and Methods:

Patients and study design:

This research is a randomized controlled clinical trial that was conducted from July 2016 to February 2019. The trial included 34 patients who underwent elective primary on-pump isolated coronary artery bypass grafting (CABG). We included adult patients (age ranged from 21 to 60 years), the body mass index (BMI) should be > 20 kg/m2 and < 34 kg/m2, and the American Society of Anesthesiologists (ASA) physical status Grade II and III. We excluded patients with left ventricular ejection fraction (EF) < 40%, pre-existing atrial fibrillation (AF), recent myocardial infarction (MI), unstable angina, carotid stenosis (> 80%), and renal impairment (creatine >200 mmol/L). Additionally, we excluded patients who had redo CABG or CABG with other concomitant procedures.

Randomization and grouping

We generated random blocks using computer software, and we randomly assigned the patients into two groups. Group (ICCC) (n= 17) received intermittent antegrade cold crystalloid cardioplegia and Group (IWBC) (n= 17) received intermittent antegrade warm blood cardioplegia.

Operative steps

Anesthesia protocol and monitoring were the same in both groups. We used a transesophageal echocardiography probe in all patients. All patients had CABG through a median sternotomy incision and aortocaval cannulation. Cardiopulmonary bypass priming was similar in both groups. Coronary artery bypass surgery was performed using the left internal mammary artery graft (LIMA) to the left anterior descending artery (LAD) in all patients, and saphenous vein grafts to the right coronary artery and/or to the left circumflex artery branches. Distal anastomoses were constructed during the total aortic cross-clamp on the arrested heart. Proximal anastomoses were performed by partial side-bite clamping of the ascending aorta with the heart beating. Additional analgesia was administered according to the individual requirements of each patient. Inotropic support was routinely used.

Cardioplegia protocol

The route of delivery was exclusively antegrade in both groups. Antegrade cardioplegia was injected directly into the aortic root at 60 to 100 mmHg pressure immediately after aortic cross-clamping and until cardiac arrest had been achieved. The heart usually arrested within 30 to 60 seconds; delay indicated problems with the delivery of the solution or unrecognized aortic regurgitation.

Table 2: Operative data in both study groups. Continuous data are presented as mean± SD and categorical variables as number and percent

Variables	ICCC group (n=17)	IWBC group (n=17)	*p* value
CPB time (min)	79.0 ± 8.7	82.9 ± 11.0	0.255
Aortic cross-clamp time (min)	38.8 ± 10.8	45.5 ± 12.1	0.102
Volume of cardioplegic solution (ml)	1294.1 ± 356.1	1658.8 ± 490.8	0.019
Time to regain NSR (min)	7.06 ± 1.8	2.17 ± 0.8	<0.001
Reperfusion arrhythmia			
Atrial	2 (11.8%)	1 (5.9%)	0.545
Ventricular	6 (35.3%)	1 (5.9%)	0.03
Number of DC shocks	5 (29.4%)	2 (11.8%)	0.22

ICCC: intermittent cold crystalloid cardioplegia; IWBC: intermittent warm blood cardioplegia; CPB: cardiopulmonary bypass; NSR: normal sinus rhythm.

Table 3: Intraoperative biomarkers of myocardial injury in both study groups. Continuous data are presented as mean± SD.

Study Group	Coronary sinus pH			*P* value	Coronary sinus lactate (mmol/l)			*p* value
	Pre-XCL	XCL off	Rep		Pre-XCL	XCL off	Rep	
ICCC	7.40 ± 0.03	7.52 ± 0.02	7.46 ± 0.03	<0.001	0.79 ± 0.10	0.79 ± 0.10	1.56 ± 0.41	0.043
IWBC	7.39 ± 0.02	7.34 ± 0.03	7.37 ± 0.02		0.78 ± 0.09	0.78 ± 0.09	2.13 ± 1.04	

ICCC: intermittent cold crystalloid cardioplegia; IWBC: intermittent warm blood cardioplegia; Pre-XCL: before aortic clamping; XCL off: 1 min after removal of the clamp; Rep: 15 min after reperfusion.

Intermittent antegrade cold crystalloid cardioplegia:

We used Thomas cardioplegia solution in the following concentration in mEq/L (K = 16, Ca = 1.2, Na = 110, Cl = 160, Hco3 = 10). We administered intermittent antegrade cold (4 °C) crystalloid cardioplegia in a dose of 10 mL/kg, followed by a half dose every 25–30 minutes at a pressure of 60-100 mmHg over 3-4 minutes. Myocardial protection was completed by additional topical cardiac cooling using ice slush and repeated when the slush had melted. Systemic cooling was held to 30°C. The mean number of cardioplegia doses was 1.59±0.71.

Intermittent antegrade warm blood cardioplegia:

We infused normothermic blood cardioplegia containing K+ in a concentration of 2 mEq/ml into the aortic root. The temperature of the perfusate was34–35 °C, and the first dose was 600 mL, followed by doses of 400 mL each over 2 minutes every16–20 minutes. The mean number of cardioplegia doses was 1.94±0.56.

Ethical issues:

Written informed patient consent was obtained from all patients before enrollment. The study was conducted in accordance with the guidelines of the Helsinki Declaration on human experimentation. Patients retained the right to refuse enrollment or withdraw from the study. The study presented minimal harm since both types of cardioplegia were in clinical use.

Data collection and endpoints:

Participant characteristics (demographics and clinical features) were recorded. Procedure characteristics, including cardiopulmonary bypass and aortic cross-clamp times, reperfusion-induced arrhythmia (supraventricular or ventricular), and the number of direct-current shocks required to convert to sinus rhythm were identified and reported. Data related to cardioplegia were the number of doses, and total volume administered. Myocardial metabolism was assessed before aortic clamping, 1 minute after removal of the clamp, and 15 min after reperfusion. Blood samples were collected from coronary sinus by the surgeon. Blood samples were analyzed for pH and lactate.

Table 4: Clinical indicators of intraoperative myocardial injury. Continuous data are presented as mean± SD and categorical variables as number and percent.

Variables	ICCC group (n=17)	IWBC group(n=17)	*p* value
ECG changes			
ST-elevation	4 (23.5%)	3 (17.6%)	0.678
ST-depression	2 (11.8%)	1 (5.9%)	
New Qs	0	1 (5.9%)	
LVEF (%)			
15 minutes after CPB	55.06 ± 9.18	55.53 ± 10.06	0.3
Sternal closure	55.53 ± 9.44	57.41 ± 11.18	

ICCC: intermittent cold crystalloid cardioplegia, IWBC: intermittent warm blood cardioplegia, LVEF: left ventricular ejection fraction, CPB: cardiopulmonary bypass.

Both creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI) levels were evaluated in peripheral blood at 6, 12, and 24 hours postoperatively.

Intraoperative myocardial ischemia was detected by the occurrence of new segmental wall motion abnormalities (SWMAs) using two-dimensional transesophageal echocardiography (TEE) and/or ST-segment changes on ECG.

Hemodynamic data were obtained, including absolute values of mean arterial pressure (MAP) and heart rate (HR). Left ventricular function was assessed using transesophageal echocardiography. For all patients, baseline measurements were recorded after skin incision. Recordings were also made 15 minutes after cessation of cardiopulmonary bypass and after sternal closure.

Low output syndrome (LOS) was defined as the need for high dose inotropic support (epinephrine > 0.05 µg kg/min) or intra-aortic balloon pump (IABP) counterpulsation for ≥60 minutes in association with systolic blood pressure <90 mm Hg.

Stroke, atrial fibrillation (AF), the need for new renal dialysis, hospital, and intensive care unit stays were recorded.

Statistical analysis:

The statistical analysis was performed using IBM SPSS Statistics® 22 for Windows 10 operating system (IBM Corp, Chicago, IL, USA). Descriptive data were expressed as mean and SD for continuous variables, and number and percentages (%) for dichotomous and categorical variables. Continuous data were compared between both groups using the t-test or Mann-Whitney test. Categorical data were analyzed using the Chi-square or Fisher exact test when appropriate.

Repeated measures one-way analysis of variance (ANOVA) was used to analyze the continuous, repeatedly measured variables. The level of statistical significance was considered to be $p<0.05$.

Results

Preoperative data:

Demographic (age, gender, BMI) and clinical (ASA, comorbidities, number of diseased vessels, preoperative wall motion abnormalities, and ejection fraction) characteristics were similar in both groups (Table 1).

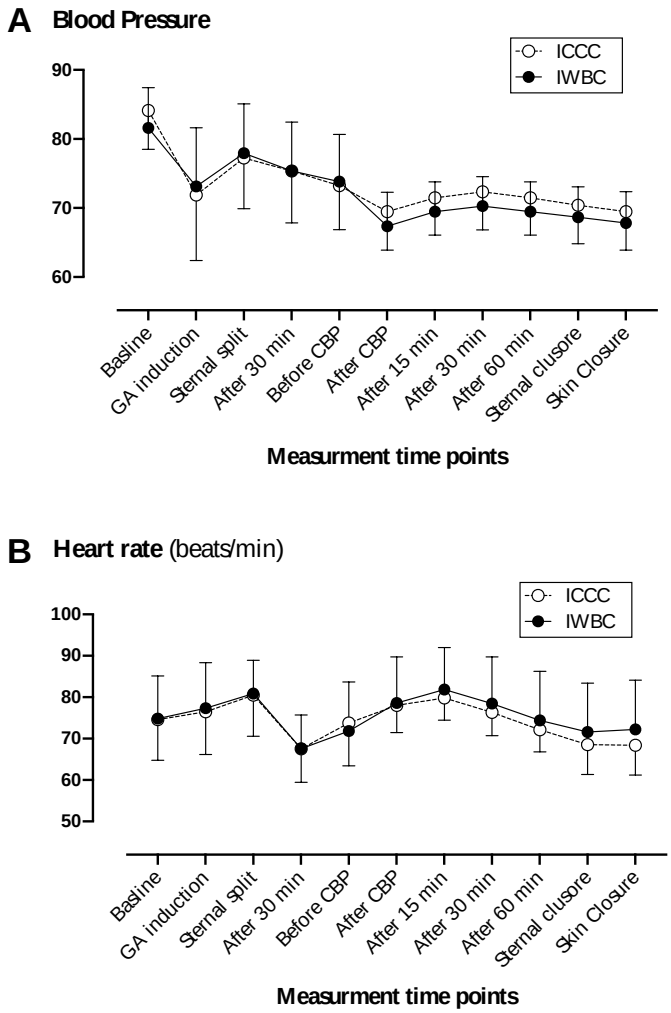

Figure 1: Intraoperative mean arterial blood pressure (MAP) and heart rate (HR) at different time points in both study groups. ICCC: intermittent cold crystalloid cardioplegia; IWBC: intermittent warm blood cardioplegia; CPB: cardiopulmonary bypass

Procedure data:

The total volume of cardioplegic solution was significantly higher in the warm blood group. Both bypass and cross-clamp times were non-significantly different between both groups. The time taken to regain normal sinus rhythm was

Table 5: New segmental wall motion abnormality. Categorical variables are presented as number and percent.

NSWMAs	ICCC group (n=17)	IWBC group (n=17)	*p* value
15 minutes after CPB			
Mild hypokinesia	1 (5.9%)	2 (11.8%)	
Severe hypokinesia	3 (17.6%)	2 (11.8%)	0.665
Akinesia	0	1 (5.9%)	
Sternal closure			
Mild hypokinesia	1 (5.9%)	2 (11.8%)	
Severe hypokinesia	2 (11.8%)	2 (11.8%)	0.685
Akinesia	0	1 (5.9%)	

NSWMAs: new segmental wall motion abnormalities; ICCC: intermittent cold crystalloid cardioplegia; IWBC: intermittent warm blood cardioplegia; CPB: cardiopulmonary bypass.

significantly longer in the cold crystalloid group with a significantly higher incidence of reperfusion ventricular arrhythmia (35% versus 6%) compared to the warm blood group (Table 2).

Study outcomes:

Mean arterial blood pressure and heart rate were non-significantly different between both groups at all intraoperative time intervals (p= 0.7 and 0.95, respectively) (Figure 1A and B).

Both coronary sinus acid production and lactate level were significantly higher in the warm blood group than in the cold crystalloid group at 1 minute after removal of the clamp and 15 min after reperfusion (Table 3). The intraoperative ECG changes were non-significantly different between both groups. Moreover, the means of left ventricular ejection fraction were non-significantly different between both groups 15 minutes after bypass and after sternal closure (Table 4).

The intraoperative occurrence and severity of new segmental wall motion abnormalities were non-significantly different between both groups 15 minutes after bypass and after sternal closure (Table 5).

Both creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI) levels were non-significantly different between both groups at all postoperative time points (at 6, 12, and 24 hours) (Table 6).

The postoperative outcomes, including; the vasoactive drug use, adverse cardiac events, and ICU and hospital stay, were non-significantly different between both groups. One patient (6%) died because of postoperative MI and low cardiac output syndrome in the warm blood group (Table 7).

Discussion

Adequate myocardial protection is the main target of the cardioplegic arrest. Despite the ongoing research, the optimal cardioplegic solution has not been reached yet.

Table 6: Postoperative biomarkers of myocardial injury. Continuous data are presented as mean± SD.

Study Group	CK-MB (U/l)			*p* value	Troponin I (ng/ml)			*p* value
	6 h	12 h	24h		6 h	12 h	24h	
ICCC group (n=17)	79.58 ± 6.29	70.88 ± 6.65	60.76 ± 7.49	0.46	0.782 ± 0.09	0.724 ± 0.10	0.379 ± 0.05	0.37
IWBC group (n=17)	76.35 ± 6.67	66.29 ± 10.17	59.11 ± 16.82		0.812 ± 0.19	0.764 ± 0.20	0.438 ± 0.25	

ICCC: intermittent cold crystalloid cardioplegia; IWBC: intermittent warm blood cardioplegia.

Table 7: Postoperative hospital outcomes in both study groups. Continuous data are presented as mean± SD and categorical variables as number and percent.

	ICCC group (n=17)	IWBC group (n=17)	P-value
Hemodynamic support			
Inotropes	11 (64.7%)	6 (35.3%)	0.086
Vasopressors	5 (29.4%)	4 (23.5%)	0.697
Adverse cardiac events			
Death	0	1 (5.9%)	0.310
Postoperative MI/CHF	0	1 (5.9%)	0.310
AF	0	1 (5.9%)	0.310
Need for IABP	0	1 (5.9%)	0.310
Postoperative stay			
Stay in ICU (days)	2.29 ± 0.77	2.41 ± 0.87	0.678
Stay in hospital (days)	9.28 ± 0.76	9.42 ± 0.88	0.623

AF: atrial fibrillation; ICCC: intermittent cold crystalloid cardioplegia; IWBC: intermittent warm blood cardioplegia; CHF: congestive heart failure; IABP: intra-aortic balloon pump; ICU: intensive care unit; MI: myocardial infarction.

We performed a clinical trial on patients undergoing elective primary on-pump isolated CABG, comparing intermittent cold crystalloid cardioplegia (ICCC) or intermittent warm blood cardioplegia (IWBC). The primary objective of this study was to assess the impact of administration of each cardioplegia solution on myocardium metabolism assessed by lactate level measured in coronary sinus blood.

In our study, both groups were matched regarding age, gender, BMI, ASA class, comorbidities, number of diseased vessels, segmental wall motion abnormality, and left ventricular ejection fraction. Coronary sinus lactate level and acid production were significantly greater in the warm blood group than in the cold crystalloid group at 1 minute after removal of the aortic cross-clamp and at 15 min after reperfusion. Several studies showed that warm cardioplegia was associated with greater lactate production than cold cardioplegia [10, 11]. Borowski and coworkers reported a lower lactate release and higher pH with cold cardioplegia [12].

A meta-analysis reported no statistically significant difference between blood cardioplegia and crystalloid cardioplegia concerning lactate levels at any measured time point [13]. The results of the meta-analysis can be explained by the fact that the analysis included studies on pediatric patients; however, all studies compared cold crystalloid to cold blood cardioplegia.

In the current study, we found that the total volume of cardioplegic solution was significantly higher in the warm blood group. However, both bypass and cross-clamp durations were non-significantly different between both groups. On the other hand, the time taken to regain normal sinus rhythm was significantly longer in the cold crystalloid group with a substantially higher incidence of reperfusion ventricular arrhythmia compared to the warm blood group. Nardi and associates found that the mean doses of cardioplegia were higher in the warm blood group, while cardiopulmonary and aortic cross-clamp times were similar in both groups [14].

In our study, we reported that both heart rate and arterial blood pressure were comparable between both groups. Additionally, we found that the intraoperative ECG ischemic changes and the left ventricular ejection fraction after bypass and after sternal closure were non-significantly different between both groups. Moreover, we demonstrated that the intraoperative incidence and severity of new segmental wall motion abnormalities were comparable between both groups.

Several studies reported no change in EF with different types of cardioplegic solutions [14, 15]. Poncelet et al. performed a randomized study to compare warm blood and cold crystalloid

cardioplegia. They reported no difference in EF between the two groups [16].

Nardi and colleagues reported that postoperative EF was better in the cold cardioplegia group [17]. This difference in their findings compared to our study could be explained by the fact that their study included primarily patients undergoing aortic valve replacement. In the CABG Patch Trial, patients with an EF of <36% were assigned to blood or crystalloid cardioplegia [18]. They found that ventricular dysfunction was less with normothermic blood cardioplegia than cold blood cardioplegia. The difference in their findings compared to ours could be related to the patients' selection; the Patch trial included patients with low EF, while we excluded those patients.

In our study, we reported that both creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI) levels were comparable between both groups. Moreover, we found that all postoperative outcomes, including; the vasoactive drug use, adverse cardiac events, and ICU and hospital stay, were comparable between both groups. A meta-analysis found no difference in mortality, MI, and low cardiac output between the blood and crystalloid cardioplegia [19].

Similarly, Nardi and coworkers reported similar serum levels of myocardial enzymes after CABG in patients who had cold and blood cardioplegia. Additionally, they reported similar clinical outcomes in both groups. However, postoperative paroxysmal atrial fibrillation was higher in the warm blood group, although this difference did not reach a statistically significant level [17].

In contrast to the current study, Mourad and collaborators [15] found a highly significant decrease in the release of cardiac enzymes after 24 hours in patients who received warm blood cardioplegia. The reduction of the myocardial release of cTnI was highly significant immediately postoperative, 12, and 24 hours after arrival to ICU.

Similarly, Franke and associates reported lower CK-MB and cTnI levels with warm blood cardioplegia [20]. However, they had a longer bypass time in the cold crystalloid group, which could lead to higher enzyme levels. Vermes and collaborators reported that cTnI concentration was closely correlated to cardiopulmonary bypass and aortic cross-clamping times [21].

Guru and coworkers reported a significant increase in CK-MB release with cold crystalloid cardioplegia in a meta-analysis of 34 clinical trials [1]. The difference in the results of this review compared to ours can be explained by the different components of blood and crystalloid cardioplegia solutions that were used by different investigators.

On the other hand, De Jonge and coworkers found higher CK-MB levels in patients who had blood cardioplegia [22]. The type of cardioplegia did not influence early mortality, postoperative low cardiac output syndrome, or intensive care unit stay.

In summary, our study found that myocardial metabolism is reduced with the use of cold crystalloid cardioplegia compared to the warm blood solution; however, this reduction was not translated into a difference in the clinical outcomes.

Limitations

The major limitation of this study was the sample size. We were able to detect a difference in cardiac metabolism between both cardioplegic solutions; however, the sample size may not be enough to detect a difference in the clinical outcomes. Another limitation is the short follow-up period, and a longer and larger study is recommended. Additionally, this study represents a single-center experience, and generalization of the results may not be applicable to all centers. The results of the study may be affected by the composition of the cardioplegic solutions, and different components may yield different results.

Conclusion

Intermittent antegrade cold crystalloid cardioplegia was associated with attenuated myocardial metabolism. However, it was associated with a longer time to regain normal

sinus rhythm and more reperfusion ventricular arrhythmias. We did not find differences in the clinical and echocardiographic outcomes and cardiac enzymes between cold crystalloid and warm blood cardioplegia.

Conflict of interest: Authors declare no conflict of interest.

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