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BNP, TnI and Lactic Acid variations in Warm Blood Cardioplegia vs Cold Crystalloid Cardioplegia in Coronary Artery Bypass Grafting (CABG)

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ABSTRACT
Introduction: Myocardial protection is one of the key points during cardiac surgery. Inadequate myocardial protection in cross-clamping period is an issue of concern in cardiac surgery. Cardioplegic solutions improve the tolerance of ischemia and reperfusion by preserving myocardial energy reserves, preventing osmotic, electrolyte imbalances and acidosis.
Warm blood cardioplegia (WBC) has had a profound impact, especially in coronary artery bypass surgery and there have been many studies that compared it with Cold crystalloid cardioplegia (CCC). A good myocardial protection will be reflected especially on patients outcome, on postoperative ICU strategy, morbidity and mortality as well.
Brain Natriuretic Peptide (BNP), Troponin I (TnI) and Lactic Acid LA) are very significant biomarkers that reflects an adequate myocardial and organ perfusion/protection.
The purpose of this study is to determine if warm blood cardioplegia offers any advantages in comparison with CCC in Coronary Artery Bypass Grafting (CABG) based primary on variations of BNP, TnI and Lactic Acid.
Patients and method: 60 patients with coronary artery disease (CAD) that will have Coronary Artery Bypass Surgery (CABG), were retrospectively randomized in two groups of 30 patients with different techniques of myocardial protection: group A had CCC, and group B had warm blood cardioplegia (WBC), according to Calafiore [1] protocols).
Intraoperative and postoperative variables were used to assess primary outcomes.
Results: This study found benefits of warm blood cardioplegia in clinical outcome after CABG
Keywords:Myocardial protection, Cardiac surgery, Cardiopulmonary Bypass, Calafiore, Cardioplegia, Coronary Artery Bypass Grafting (CABG), Brain Natriuretic Peptide (BNP), Troponin I (TnI) and Lactic Acid LA)
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INTRODUCTION

Myocardial protection during cardiac surgery is the key point in this kind of intervention[1,2]. The different techniques of myocardial protection have evolved in the course of the years, making cardiac surgery much safer[1,2,3] This study is a part of several years follow-up in our clinics of cardiac surgery. Since many years we changed the cardioplegia solution from crystalloid into blood, based on western clinics guidelines and conditions of our clinic. Since 2008 we use successfully warm blood cardioplegia (Calafiore cardioplegia protocol) [1] and, with very good results[4,5]

Blood cardioplegia has had a profound impact on cardiac surgery, especially in coronary artery bypass surgery [4] Warm blood cardioplegia is used to modify reperfusion injury, resulting in improved postoperative contractile function and decreased mortality [3,4,6,7,8] . Very safe predictors of good myocardial protection are BNP [9,10,11,12], TnI [12,13,14] and Lactic Acid [15,16] measured before and after Cardiopulmonary Bypass (CPB).

Brain natriuretic peptide (BNP) release is a marker of increased myocardial wall tension, which is elevated in patients with disturbed left ventricular function. As it is increasingly being used as a reliable marker for diagnosis, BNP measurement might be relevant for patients undergoing cardiac surgery for evaluating myocardial protection [9]

Troponin I is a cardiac and skeletal muscle protein family. It is a part of the troponin protein complex. It is a useful marker in the laboratory diagnosis of heart attack and also it is very useful for confirmation of cardiac muscle damage during CPB [17,18,19]. It is very well-established that TnI elevation is nearly universal after cardiac surgery procedures [19]; there are multiple mechanisms proposed to explain the finding of myocardial

injury after cardiac surgery: intra-operative injury may occur related to cardiac manipulation, inadequate myocardial protection, intra-operative defibrillation or acute post-bypass hemodynamic instability. In a recent study these mechanisms were supported as a cause of TnI elevation in the post-operative setting [19]

Lactic acid (LA) is an organic acid produced by the body when glucose (sugar) is broken down to generate Adenosine triphosphate (ATP) (cellular energy) in the absence of oxygen. Since LA [10,11] is a very good marker of systemic organ perfusion it is a very good variable to determine whether an adequate organ perfusion/protection is performed in correlation with myocardial protection [17].Januzzi JL, Lewandrowski K, MacGillivray TE. et al. A comparison of cardiac troponin T and creatine kinase-MB for patient evaluation after cardiac surgery. J Am Coll Cardiol. 2002;39:1518–1523.

The aim of this study is to determine whether warm blood cardioplegia (WBC) offers any advantages in comparison with cold crystalloid cardioplegia (CCC) in patients with CABG.

We designed a study to compare 2 techniques of myocardial protection: CCC, and WBC. The results were primarily assessed on the basis of BNP, TnI, Lactic Acid variations and also with clinical outcome and postoperative blood loss/requirements, time of intubation, ICU.

PATIENTS AND METHODS

Between January 2012 and September 2022, in Cardiac Surgery Clinic in “Mother Theresa” Hospital Center, Tirana, Albania and Hygeia Hospital, Tirana, Albania, 30 patients, who were scheduled for CABG were enrolled in this study. In these patients was used CCC in group A.

In the same period we retrospectively randomized 30 other patients in the same clinics, who like the above mentioned group were scheduled for CABG. In those was used WBC Group B.

Anesthesia techniques were the same in both groups, endotracheal TIVA Anesthesia.

In group A, intermittent antegrade cold crystalloid cardioplegia (CCC) (2-5 grade C) was used.

In group B, was used warm blood cardioplegia (WBC according to Calafiore protocols) (33-35°C as the systemic CPB temperature was delivered)

Initial power calculations were supported by the presence of preliminary data, defining the effect of WBC vs CCC on CABG.

Sixty patients with coronary artery disease CABGx3, 60-70 years old, males and females in the same number, Body Surface Area (BSA) 1.79-1.88m², with normal ejection fraction (EF) (50-65%), normal Pulmonary Arterial Systolic Pressure (PSAP in mmHg), with similar risk factors and co-morbidities, in sinus rhythm, New York Heart Association (NYHA I-II), EuroSCORE II (European System for Cardiac Operative Risk Evaluation) were retrospectively randomized in two groups of 30 patients.

In each group we applied one technique of myocardial protection Group A we applied CCC and in Group B we applied WBC

The study was approved by our Institutional Ethics Committee, and informed consent of the patients was obtained.

All operations were performed using cardiopulmonary bypass (CPB) with ascending aortic and right atrium cannulation. Systemic moderate hypothermia was between 33°C and 35°C in Group A and in Group B.

In group A, antegrade intermittent cold crystalloid cardioplegia was injected immediately after aortic cross-clamping at 15-20mL·kg^{-1} and then at 30 minutes intervals..

In Group B, the technique WBC was realized according to the Calafiore protocols. Antegrade intermittent Warm Blood cardioplegia was performed after aortic cross-clamping at 15-20mL·kg-1 and then at 20 minutes intervals. The WBC temperature was gradually increased from 33°C to 36°C by the end of the operation.

In both groups, electrical defibrillation was applied if ventricular fibrillation persisted beyond 2min after aortic declamping, and a temporary pacemaker was used if there was no spontaneous rhythm or if the patient’s heart rate was less than 50 beats·min-1. After the operation, if systolic blood pressure was lower than 90 mm Hg and urine output less than 1 mL·kg-1·h-1 with central venous pressure between 10 and 12 mm Hg, inotropic support was started. Our first choice of inotropic agent was norepinephrine and milrinone.

Intraoperative and postoperative variables were used to assess primary clinical outcomes.

As primary intraoperative variables we assessed BNP, TnI and Lactic Acid levels immediately before, after CPB and 12 hours after CPB. We also included hematocrit levels before and after CPB period, spontaneous rhythm recovery after aortic declamping, requirement for electrical defibrillation or temporary pacemaker, maximum doses of inotropes, duration of inotropic support, postoperative ejection fraction, length of intensive care unit stay, postoperative blood loss and blood requirements.

Markers of the selected intra- and postoperative variables are shown as the mean, standard deviation of the mean, and median. The similarity of the mean and median conferment a Gaussian normal distribution of all clinical parameters. Analysis of the difference in clinical outcomes between the two groups was performed using Student’s t test.

The statistical significance level for differences was $p < 0.05$.

Table 1. Preoperative and Operative Data in Patients Undergoing CABG

	Group A (n = 30)			Group B (n = 30)			
Variables	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**p-value***
Age	66.67	3.45	67	67.53	3.56	68	0.3985
Gender (M/F)	0.47**			0.50**			
ACC (min)	74.23	7.6	75.93	75.93	7.78	76.0	0.3919
RT (min)	25.43	2.63	25.0	21.33	2.29	21.5	**<0.001*** **
CPB (minutes)	103.67	9.96	104.0	101.27	9.89	102.0	0.3490
T-CPB (c°)	34.37	0.54	34.0	34.15	0.65	34.0	0.1487
IS Yes-1 No-0	0.73			0.07			**<0.001**
ICS (days)	2.48	0.45	2.5	1.18	0.33	1.5	**<0.001**
BL (ml)	372	68.67	370	253.3	48.87	255.0	**<0.001**
BT (units)	1.33	1.65	1.0	0.3	0.53	0.0	**0.0024**

Age (years)
Gender Male/Female (1/0)
ACC Aortic cross clamp (minutes)
RT Reperfusion time (minutes)
CPB Cardiopulmonary bypass (minutes)
T-CPB Temperature during CPB (°C)
IS Inotropic support Yes-1 No-0
ICS Intensive care stay (days)
BL Blood loss (ml)
BT Blood transfusion (number of units)

* Two-tailed Student T-Test. If p-value is < 0.05, there is a statistically significant difference of the means of the two groups for each clinical outcome

**These are proportions with the clinical outcome present (Yes) within each group. Z-test is used to measure statistical significance of their differences.

*** In 'bold' statistically significant differences

Table 2. Comparison of Clinical Outcomes

	Group A			Group B			
Variables	Mean	SD	Median	Mean	SD	Median	p-value*
BNP b-CPB pg/ml	69.27	12.68	69	66.93	10.41	67.5	0.4391
BNP a-CPB pg/ml	153.13	18.88	149.5	114.9	12.81	116	**<0.001*** **
TnI b-CPB ng/ml	0.2	0.1	0.2	0.2	0.1	0.2	0.9760
TnI a-CPB ng/ml	0.97	0.23	0.97	0.45	0.1	0.47	**<0.001**
TnI a-12-CPB ng/ml	6.06	1.54	6.32	2.15	0.64	2.13	**<0.001**
LA b-CPB mg/dl	0.22	0.07	0.21	0.2	0.06	0.19	0.3640
LA a-CPB mg/dl	1.69	0.27	1.71	1.15	0.19	1.13	**<0.001**
LA a-12-CPB mg/dl	1.72	0.33	1.64	0.94	0.17	0.99	**<0.001**
Hct b-CPB (%)	42.8	4.21	42.5	40.4	3.86	40.5	0.025
Hct a-CPB (%)	30.97	2.51	30.0	33.2	2.46	33.5	**<0.001**
SRR Yes-1 No-0	0.27**			1.00**			**<0.001**
VF-a-ad Yes-1No-0	0.87			0.07			**<0.001**
Df-a-ad Yes-1No-0	0.87			0.07			**<0.001**
T_PM Yes-1 No-0	0.73			0.07			**<0.001**

BNP-b Brain Natriuretic Peptide pg/ml before CPB
BNP-a Brain Natriuretic Peptide pg/ml after CPB
TnI-b Troponin I ng/ml before CPB
TnI-a Troponin I) ng/ml after CPB
LA-b Lactic Acid mg/dl mmol/L before CPB
LA-a Lactic Acid mg/dl mmol/L after CPB
LA-a-12 lactic Acid after 12 hours after CPB
Hct-b Hematocrit before CPB (%)
Hct-a Hematocrit after CPB (%)
SRR Spontaneous rhythm recovery Yes-1 No-0
VF-a-ad Ventricular Fibrillation after aortic declamping Yes-1 No-0
Df-a-ad Defibrillation/Rhythm conversion after Aortic Declamping Yes-1 No-0
T-PM Temporary pacemaker Yes-1 No-0

* Two-tailed Student T-Test. If p-value is < 0.05, there is a statistically significant difference of the means of the two groups for each clinical outcome

**These are proportions with the clinical outcome present (Yes) within each group. Z-test is used to measure statistical significance of their differences.

*** In 'bold' statistically significant differences.

RESULTS

There were no preoperative or operative differences between the two groups with regard to age, sex, New York Heart Association functional class, Euroscore II, systolic pressure, duration of the operation, CPB, aortic cross-clamping and reperfusion, surgical technique (Table 1).

There was no death in our series.

Clinical outcomes are shown in Table 2.

There is a significant difference ($p<0.001$) in the BNP, TnI and Lactic Acid levels with the superiority of group B

This significance persisted even after 12 hours of operation in the TnI and LA levels

The changes in hematocrit level differs significantly between the two groups on the post CPB period (p=0,001)

There appeared to be a trend towards better spontaneous recovery of sinus rhythm after removal of the aortic cross-clamp in group B compared with group A, the difference did reach statistical significance ($p<0.01$).

According to our protocol for postoperative care, group B did not require inotropic support postoperatively. There were differences between the 2 groups in inotropic support (P=0.001) with superiority in group B

There is also a significant difference regarding the necessity of defibrillation and placement of temporary pace maker after aortic declamping, with superiority in group B (p=0.001)

We also found a significant difference between two groups in reperfusion time, intensive care stay, blood loss/transfusion, with superiority of group B ($p<0.05$)

Postoperative echocardiography showed a slight decrease of left ventricular ejection fractions in both groups, only at the first postoperative day, which was improved in the consecutive days.

DISCUSSION

The basic concept of WBC is reduction of myocardial energy demand by maintaining cardiac arrest with hyperkalemic warm blood perfusion during initial reperfusion, to restore high-energy phosphates and enhance cellular repair after ischemic cardiac arrest [4,6]

The beneficial effects of WBC have been studied both experimentally and clinically[20]. They include better preservation of high-energy phosphates and endogenous amino acids, less anaerobic metabolic activity on reperfusion, reduced release of cardiac troponin T, and improved post-ischemic functional recovery [4,7,19]. These effects facilitate coronary vasodilatation and accelerate early myocardial tissue oxygen saturation during warm reperfusion [6,7,8,]

Tenpaku and colleagues [6] demonstrated complete microtubule repolymerisation after 10 min of reperfusion with warm blood. This mechanism may be responsible for the early and improved recovery of cardiac function associated with WBC.

Most clinical studies of MWBC have been undertaken on coronary artery bypass surgery, with more recent investigations on WBC in congenital heart surgery [3,4,19].

Most results have showed definite advantages in the use of WBC[20]

Modi and colleagues [20] demonstrated a superior biochemical outcome from WBC in patients with longer cross-clamp times.

In this study, the mean cross-clamp time was more than 50 min, which may have been long enough to demonstrate the advantage of WBC. The duration of WBC infusion may be an important factor[5,7].

There is some evidence that a glutamate-aspartate supplement to the WBC (substrate-enriched

Cardioplegia) may reduce reperfusion injury and improve both metabolic and myocardial function recovery[6,7]. Glutamate and aspartate are not available at our institute, so our WBC was not a substrate-enriched solution, and it is possible that the WBC benefits would be more obvious if this technique was employed. Improved spontaneous rhythm recovery has also been observed with the use of WBC [8] It appeared to be a trend towards a better cardiac rhythm recovery in the WBC group (less requirement of electrical defibrillation and temporary pacemakers), the difference did reach statistical significance when compared with patients in the CCC group ($p<0.05$).

BNP, Troponin I and Lactic Acid are unique biochemical markers of myocardial damage because of their high level of sensitivity and specificity. These characteristics make BNP and Troponin I ideal markers for myocardial cell damage in patients undergoing cardiac surgery, and also Lactic acid an ideal biomarker for organ perfusion/protection and useful for comparison of different myocardial protective techniques during cardiac operations[15,16].

Conclusion: Based in our study and literature, we concluded that in CABG, WBC has advantages compare to CCC. BNP, TnI and LA variations during CPB are very safe biomarkers in predicting myocardial protection.

Keywords: Myocardial protection, Cardiac surgery, Cardiopulmonary Bypass, Calafiore, Cardioplegia,

Coronary Artery Bypass Grafting (CABG), Brain Natriuretic Peptide (BNP), Troponin I (TnI) and Lactic Acid LA)

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