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ORIGINAL ARTICLES

Troponin I, and Lactic Acid variations, during Cardiopulmonary Bypass under Moderate Hypothermia vs Normothermia.

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Abstract

Introduction: In open heart surgery such as Coronary artery Bypass Grafting, valve repair or replacement, or some congenital heart disease, patients are connected to the Cardiopulmonary bypass machine [1]. Cardiopulmonary bypass machine pumps the blood around the body while the heart is stopped and provides a bloodless field during cardiac surgery. Since an extracorporeal circuit is incorporated to the patient, there are observed abnormal physiological events during Cardiopulmonary bypass. These events include hemodilution, interstitial fluid accumulation, complement activation and depression of immune system. Cardiopulmonary bypass is associated with an acute phase reaction of protease cascades, leucocyte, and platelet activation that result in tissue injury [2, 3] and limited functional reserve. For many years was believed that Cardiopulmonary bypass under hypothermia is much safer. The main reason for "cooling body" is to protect the brain, heart and organs during cardiopulmonary bypass through reducing body metabolic rate [4]. During more recent years, according to many studies, it is shown that Cardiopulmonary bypass under Normothermia has much more advantages compared to Moderate Hypothermia.

The aim of this study was to compare and examine which method has advantages in terms of clinical outcome, morbidity and mortality.

Patients and methods. 60 patients were selected, who were scheduled for Coronary artery Bypass Grafting x 3, were enrolled in this study.

Results: According to the primary variables (Troponin I, Lactic Acid) and also secondary variables of our study, resulted that Cardiopulmonary bypass in Normothermia has superiority compare to Moderate Hypothermia in patients that underwent Coronary artery Bypass Grafting.

Conclusion: According to our data and literature [15, 16, 17], we concluded that Cardiopulmonary bypass in Coronary artery Bypass Grafting under Normothermia has advantages vs Moderate Hypothermia and Troponin I and Lactic Acid are very good biomarkers that show us if heart and organs perfusion/protection is adequate during this procedure.

Keywords: Cardiopulmonary Bypass, Moderate Hypothermia, Normothermia, Cardiac Surgery, Coronary artery Bypass Grafting, Troponin I, Lactic Acid.

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Abbreviations

CPB - Cardiopulmonary bypass; CABG - Coronary artery Bypass Grafting; CS - Cardiac Surgery; NT - Normothermia ; MHT - Moderate Hypothermia; TnI - Troponin I; LA - Lactic Acid; ATP - Adenosine Triphosphate; CAD - Coronary Artery Disease; BSA - Body Surface Area; PSAP - Pulmonary Systolic Arterial Pressure; EF - Ejection Fraction; TIVA - Total Intravenous Anaesthesia; ACC - Aortic Cross Clamp; RT - Reperfusion Time; IS - Inotropic Support; ICS - Intensive Care Stay;BL - Blood Loss; BT- Blood Transfusion; Hct - Hematocrit

Introduction:

The first successful human cardiac surgery using CPB was performed by John Gibbon in 1952[1] for repair of the atrial septal defect. The safe conduct of CPB requires a team effort between the surgeon, perfusionist and anesthesiologist [1].

In open heart surgery such as CABG, valve repair or replacement, or some congenital heart disease, patients are connected to the CPB machine. CPB machine pumps the blood around the body while the heart is stopped and provides a bloodless field during cardiac surgery. Since an extracorporeal circuit is incorporated to the patient, there are some abnormal physiological events during CPB [1]. These events include hemodilution, interstitial fluid accumulation, complement activation and depression of immune system [2, 3].

CPB is associated with an acute phase reaction of protease cascades, leucocyte, and platelet activation that results in tissue injury [2, 3].

This is largely manifested as subclinical organ dysfunction that produces a clinical effect in those patients that generate an excessive inflammatory response or in those with limited functional reserve. The contribution of myocardial ischemia/reperfusion, secondary to aortic cross-clamping, and cardioplegic arrest, to the systemic inflammatory response and wider organ dysfunction [3] require further evaluation in clinical trials.

For long it was believed that CPB under hypothermia [4] is much safer, and the main reason for the "cooling body" is to protect the brain, heart and organs during cardiopulmonary bypass through reducing body metabolic rate [4]. In more recent years, according to many studies is seen that CPB under NT has much more advantages compared to MHT [5].

Troponin I is a cardiac and skeletal muscle protein family. It is a part of the troponin protein complex. The letter I is given due to its inhibitory character. 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 [6, 7, 8, 9].

It is very well-established that TnI elevation is nearly universal after cardiac surgery procedures [7, 8, 9]. 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 one recent study, each of these mechanisms were supported as a cause of TnI elevation in the post-operative setting [9]

Lactic acid is an organic acid produced by the body when glucose (sugar) is broken down to generate ATP (cellular energy) in the absence of oxygen. Since LA [10] is a very good marker of systemic organ perfusion it is a very good variable to determine whether an adequate CPB is performed [10, 11].

The results were primary assessed measuring and observing TnI and Lactic Acid variations before CPB, after CPB and also 12 hours after CPB. These measurements gave us a very good prediction of heart and organ perfusion/protection and also on clinical outcome [11, 12, 13]

The aim of this study was to compare and examine whether CPB under NT has superiority vs CPB under MHT in terms of clinical outcome, morbidity and mortality.

Patients and methods:

Were enrolled in this study, from January 10, 2013 to December 20, 2020, in Cardiac Surgery Clinic in "Mother Theresa" Hospital Center, Tirana, Albania, and Hygeia Hospital, Tirana, Albania, 60 patients, who were scheduled for CABGx3.

Patients in the study group with CAD were selected on for age groups of 60-70 years old, their BSA within 1.8-2.0 m^2, and gender (males and females) in the same numbers, with normal ejection fraction EF, with normal PSAP, with similar risk factors and co-morbidities, NYHA I-II, European System for Cardiac Operative Risk Evaluation II (Euro score II) <1.

Results:

In our study we applied two ways of maintaining body temperature during CPB. The first method is that blood is cooled 30-33ºC (MHT) and warmed to normal body temperature once the operation has been completed and the second one is that the blood is kept around 34-35ºC (NT).

They were retrospectively randomized in two groups of 30 patients Group A and Group B.

The CPB in Group A was performed under MHT and in group B under NT.

We used endotracheal TIVA anesthesia techniques for both groups

Extracorporeal Cardiopulmonary Bypass machines were roller pumps, *Terumo or Maquet models.*

In both groups we applied Warm Blood Cardioplegia (33-35°C), based in *Calafiore protocols* [14].

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

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 $p < 0.05$.

Usage of inotropic support after CPB in group A is higher than group B, in which almost all the patient had no necessity of inotropic support after CPB (p=0.039) (Tab. 1)

	Group A (n = 30) MHT			*Group B (n = 30) NT*			
Variables	***Mean***	***SD***	***Median***	***Mean***	***SD***	***Median***	***p-value****
Age	6 6.67	3.45	67	67.53	3.56	68	0.40
Gender (M/F)	0.5**			0.5			
ACC (min)	74.23	7.48	75	75.93	7.78	76.0	0.39
RT (min)	25.43	2.58	25.0	21.33	2.29	21.5	**<0.001*** **
CPB (minutes)	103.67	9.8	104.0	101.27	9.89	102.0	0.35
IS Yes-1 No-0	0.6			0.33			**<0.039**
ICS (days)	2.07	0.45	2.0	1.73	0.34	1.75	**<0.002**
BL (ml)	324	57.34	320	282	31.4	280	**<0.001**
BT (units)	1.1	0.76	1.0	0.7	0.7	1.0	**0.004**

Age (years)
Gender Male/Female (1/0)
ACC Aortic cross clamp (minutes)
RT Reperfusion time (minutes)
CPB Cardiopulmonary bypass (minutes)
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 1. Preoperative and intraoperative Data in Patients Undergoing CABG

	Group A (n-30) MHT			*Group B(n-30) NT*			
Variables	***Mean***	***SD***	***Median***	***Mean***	***SD***	***Median***	***p-value****
TnI b-CPB ng/ml	0.02	0.01	0.02	0.02	0.01	0.02	0.98
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	0.36
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 (%)	41.67	3.23	41	40.43	3.8	40.5	0.18
Hct a-CPB (%)	30.97	2.51	30.0	34.37	3.13	35	**<0.001**
SRR Yes-1 No-0	0.27***			0.77			**<0.001**
VF-a-ad Yes-1No-0	0.7			0.27			**<0.001**
Df-a-ad Yes-1No-0	0.7			0.27			**<0.001**
T_PM Yes-1 No-0	0.57			0.27			**<0.001**

TnI-b Troponin I ng/ml before CPB
TnI-a Troponin I ng/ml after CPB
TnI-a-12 Troponin I ng/ml 12 hours 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 Y-1 N-0
Df-a-ad Defibrillation conversion after Ao. Declamp. Y-1 N-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*
*** In 'bold' statistically significant differences*
****These are proportions with the clinical outcome present (Yes) within each group. Z-test is used to measure statistical significance of their differences.*

Table 2. Clinical Outcomes variables in Patients Undergoing CABG

Duration of inotropic support, intubation time, in, blood loss (p=0.001; Tab 1) and blood requirements [4] (p=0.0038, Tab 1), intensive care unit stay (P=0.002; Tab 1), were measured as secondary clinical outcomes and were higher in group A.
Also, pre- and post-echocardiographic findings, routine blood gases, renal function were used as secondary outcome and was seen superiority in group B.

The primary clinical results intraoperative (Tab. 2) are TnI and Lactic Acid before CPB, after CPB, 12 hours after CPB and were higher in Group A, with a significant difference (p<0.001). Intraoperative spontaneous recovery of sinus rhythm was present in almost all patients in group B and in few patients in group A (p<0.05) (Tab. 2)

Ventricular fibrillation (p<0.001) and intraoperative electric rhythm conversion/ Defibrillation (p<0.001) was higher in group A with statistical significance (Tab. 2). Also, the usage of temporary pace maker was higher in group A (p<0.01)

According to the primary and secondary variables, resulted that CPB in NT has superiority compare to MHT in patients that underwent CABG which results in decreased organ damage that occur during non-physiological body perfusion.

We found statistical significance differences in primary and secondary variables that support the advantage of Normothermia vs moderate Hypothermia in CABG.

We also found TnI and Lactic Acid very safe predictors for an adequate of heart and organs perfusion/protection during CPB.

Discussion:

Hypothermia as a cytoprotective strategy had demonstrated potential benefits in myocardial infarction and CPB in the beginning of cardiac surgery [15] Understanding how hypothermia can be of benefit is not simple as its action is mediated through complex systemic and cellular changes that can vary widely depending on underlying pathological and metabolic condition. Hypothermia is classified based on the depth of cooling from a normal body temperature of 37-38°C: mild hypothermia (32-35°C), moderate hypothermia (28-32°C) and deep hypothermia (< 28°C). While deep hypothermia has been embraced by various surgical subspecialties, the neuroprotective effect of mild to moderate hypothermia appears to be similar to deep. [16]. Thus, less drastic decreases in body temperature have been favored by other disciplines, as it is easier to cool nonsurgical patients to these target temperatures, and the risks of medical complications such as infection, arrhythmia, hypokalemia, coagulopathies and even heart failure are lower [16]. The widely held notion that hypothermia protects because lower temperatures slow metabolism is not completely accurate. Recent research has shown that hypothermia can alter a plethora of cell death and cell survival pathways including gene regulation resulting in the inhibition of apoptosis and inflammation [17] and the up-regulation of anti-apoptotic [18] or trophic factors [19].

Our discussion, which body temperature is more appropriate for heart and organ perfusion/protection, is supported by literature [20, 21, 22] and our clinical outcomes Table 1 and Table 2.

Conclusion:

According to our data and literature [15, 16, 17], we concluded that CPB in CABG under NT has advantages vs MHT and TnI and LA are very good biomarkers that show us if heart and organs perfusion/protection is adequate during this procedure.

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