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Comparison of hypothermic and normothermic cardiopulmonary bypass in patients undergoing coronary artery bypass graft surgery

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ABSTRACT

Objectives: Coronary artery bypass graft (CABG) surgery operations accompanied by cardiopulmonary bypass (CPB) are the most prominent treatment options. One of the basic application principles of the CPB system is the protection of vital organs by reducing metabolic rate and oxygen consumption with hypothermia. In this study, we aimed to investigate the effects of normothermia and hypothermia applications on clinical outcomes in CABG operations performed with CPB.

Methods: This single-center study was planned retrospectively. Patients who underwent isolated CABG operation with CPB at Şanlıurfa Mehmet Akif İnan Training and Research Hospital between January 01, 2020, and January 01, 2022, were included. A total of 120 patients, 60 of whom underwent hypothermic and 60 normothermic cardiac bypass, were included in the study after applying the exclusion criteria.

Results: There was no difference between the groups in terms of age, gender, diabetes mellitus, hypertension, left ventricular ejection fraction, and body surface area characteristics (P>0.05). In the normothermia group, urea, creatinine, direct bilirubin, and lactate levels were significantly higher in the first postoperative day blood values (P=0.003, P=0.04, P=0.028, P=0.005, and P<0.001, respectively). Positive inotropic agent requirement and defibrillation requirement after cross-clamping were significantly higher in the hypothermia group (P=0.006 and P=0.027, respectively).

Conclusions: In CABB operations performed with CPB, normothermia and hypothermia applications may have beneficial effects on different clinical situations.

Keywords: Cardiopulmonary bypass, coronary artery bypass grafting, normothermia, hypothermia, postoperative term

Coronary artery disease (CAD) is the most common form of cardiovascular disease associated with high mortality and morbidity worldwide. Coronary artery bypass graft (CABG) surgery operations accompanied by cardiopulmonary bypass (CPB) are the most prominent treatment options [1]. Cardiac surgery performed with CPB aims to have a bloodless and immobile surgical field. For this purpose, the functions of the heart and lungs are disabled, and the CPB system takes over these tasks. One of the basic

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application principles of this system is the protection of vital organs by reducing metabolic rate and oxygen consumption with hypothermia [2-4].

The principle of protection of other organs, especially the brain, by hypothermia is based on the Arrhenius equation. According to this equation, the reaction rate of chemicals is related to heat. The mechanism is the protection of cellular pH and adenosine triphosphate, delaying the pathological process following ischemia. [3-5] Thus, the metabolic needs of the body, especially critical organs such as the brain, kidney and heart, will be reduced. In addition, the risk of organ damage will decrease in cases where mean arterial pressure and perfusion are low [6-8].

Another method that can be applied in addition to hypothermia-based application is normothermic CPB. The main element of this method is that the patient's body temperature is kept within the normal temperature range during cardiac surgery and no intervention is made. It is stated that normothermic CPB reduces blood loss and decreases systemic vascular resistance, but causes cerebral venous oxygen desaturation in the first moments of perfusion [3, 8-10].

In this study, we aimed to investigate the effects of normothermia and hypothermia applications on clinical outcomes in CABG operations performed with CPB.

METHODS

This study was approved with the protocol dated 31/10/2022 and numbered HRÜ/22.21.05 of the Harran University Clinical Research Ethics Committee. In this study, which was planned retrospectively as a single center, patients between the ages of 20-85 who underwent isolated CABG operation with CPB at Şanlıurfa Mehmet Akif İnan Training and Research Hospital between January 01, 2020, and January 01, 2022, were included in the study. The patients who had undergone redo cardiac operations, emergency cases, those with a known history of lung disease, those with chronic renal failure, and those with a history of pneumonia were excluded from the study. A total of 120 patients, 60 of whom underwent hypothermic and 60 normothermic cardiac bypass, were included in the study after applying the exclusion criteria. Of the patients included in the study, those who underwent normothermic (36-37 oC) CPB were determined as Group 1, and those who underwent hypothermic (32 oC) CPB were determined as Group 2. Preoperative, intraoperative and postoperative data of the patients were obtained retrospectively from hospital records and patient files. Normothermic CPB is applied less frequently in our clinic. Therefore, when determining the sample size, when 60 patients were reached in the normothermic group, 60 patients were randomly selected from the hypothermia group within the same period using a computer program.

Collection of Research Data

Demographic data, identity information, age, gender, and smoking were determined and recorded. Their medical histories were analyzed in detail. The presence of hypertension, diabetes, and chronic obstructive pulmonary disease were recorded. In the study, the individual characteristics of the participants were height, weight, body surface area (BSA = Body surface area; surgical characteristics were perfusion flow rate (flow) ($L/m^2/min$), aortic cross-clamp time, total perfusion time and coronary graft number; preoperatively and postoperatively on the 1st day. Among the biochemical data examined are glucose, urea, creatine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, C-reactive protein (CRP); from electrolytes; sodium, potassium, calcium values and blood gas values. Lactate data and postoperative intra-aortic balloon pump (IABP) requirement, intraoperative+postoperative erythrocyte suspension (ES) transfusion, post-cross clamp defibrillation requirement, postoperative drainage amount, postoperative positive inotrope requirement, extubation duration, intensive care unit (ICU) length of stay data regarding duration of hospital stay were recorded.

Cardiopulmonary Bypass Method

The blood flow rates (Flow) of the patients included in this study during CPB were determined according to their body surface area (2.4 L/m2/min). The tubing set venous line diameter was used as 1/2-inch, and arterial line diameter was used as 3/8-inch. Arterial line pressures were kept between 150-180 mmHg on average during CPB. Active clotting time (ACT) was kept at 480 seconds and above by providing anticoagulation. 1200 mL balanced solution (Isolayte), 150 ml 20% mannitol, 5000 units heparin, and 2 g cefazolin were used as the primary solution. Normoth-

ermic blood cardioplegia solution was used in Group 1 and hypothermic blood cardioplegia solution was used in Group 2. Group 1 received normothermic (36-37 oC) CPB, and Group 2 received hypothermic (32 oC) CPB.

Statistical Analysis

Statistical evaluation was performed using the SPSS® 16.0 computer program. Means and standard deviations were calculated for continuous and ordinal data. Kolmogorov Smirnov test and Shapiro-Wilk test were used to evaluate normality distribution. Student t-test and Mann-Whitney U tests were used to evaluate normal and non-normally distributed numerical data, respectively. Frequency and percentage analyses were performed for nominal data and the Chi-square test was used for comparison. P values less than 0.05 were considered statistically significant.

RESULTS

Demographic characteristics and preoperative blood values of the patients included in the study are given

Table 1. Demographic characteristics and preoperative blood values of the patients

Variables	Normothermia (n=60)	Hypothermia (n=60)	P value
Age (years)	62.88±9.17	61.70±9.52	0.553
Female gender, n (%)	25 (41.7)	27 (45)	0.479
Smoking, n (%)	15 (25)	23 (38.3)	0.116
Hypertension, n (%)	48 (80)	53 (88.3)	0.211
Diabetes mellitus, n (%)	15 (25)	12 (20)	0.512
COPD, n (%)	5 (8.3)	7 (11.6)	0.543
Height (cm)	162.70±8.87	164.60±9.33	0.873
Weight (kg)	80.70±12.61	77.11±12.47	0.818
Body surface area (m^2)	1.90±0.18	1.86±0.17	0.631
LVEF (%)	51.01±8.11	49.85±8.22	0.784
Glucose (mg/dL)	172.65±51.26	187.28±58.24	0.486
Urea (mg/dL)	44.09±18.37	41.26±14.62	0.329
Creatinine (mg/dL)	1.01±0.46	0.90±0.30	0.067
Albumin (g/L)	33.78±7.66	33.30±7.36	0.903
ALT (IU/L)	38.58±53.20	33.75±53.36	0.857
AST (IU/L)	77.88±153.89	72.44±154.16	0.956
Total bilirubin (mg/dL)	1.98±10.51	0.90±0.92	0.109
Direkt bilirubin (mg/dL)	0.28±0.25	0.26±0.56	0.074
Sodium (mEq/L)	140.70±4.07	140.10±3.62	0.181
Potassium (mEq/L)	4.38±0.44	4.35±0.42	0.653
Calcium (mg/dL)	9.12±6.66	9.26±6.62	0.953
CRP (mg/L)	6.56±4.7	6.22±3.6	0.724
Lactate (mmol/L)	1.63±1.04	1.78±1.11	0.424

Data are show as mean±standard deviation or n (%). COPD=chronic obstructive pulmonary disease, LVEF=left ventricular ejection fraction, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRP=C reactive protein

in Table 1. There was no difference between the groups in terms of age, gender, diabetes mellitus, hypertension, LVEF, and body surface area characteristics. In addition, the preoperative blood values of the study groups were similar (P>0.05).

Operative data such as flow, cross-clamp time, total perfusion time, and number of coronary bypasses were similar between the groups. In the normothermia group, urea, creatinine, ALT, direct bilirubin and lactate levels were significantly higher in the first postoperative day blood values (P=0.003, P=0.04, P=0.028, P=0.005, and P<0.001, respectively) (Table 2).

Perioperative clinical characteristics of the patient groups are given in Table 3. There was no statistically significant difference between the groups in terms of IABP requirement rates, red blood cell suspension requirement, postoperative drainage, extubation time, ICU stay, and total hospital stay. Positive inotropic agent requirement and defibrillation requirement after cross-clamping were significantly higher in the hypothermia group (P=0.006 and P=0.027, respectively).

DISCUSSION

In CABG operations performed with cardiopulmonary bypass (CPB), intraoperative hypothermia is an integral part of CPB. Among the findings of this study, we found that intraoperative hypothermia has some advantages on postoperative clinical outcomes compared to intraoperative normothermia. We found that urea, creatinine, direct bilirubin and lactate levels were significantly lower in the hypothermia group. Also we showed that inotropic requirement and defibrillation

Table 2. Comparison of operative variables and postoperative first-day blood values of the patients

Variables		Normothermia (n=60)	Hypothermia (n=60)	P value
Glucose (mg/dL)		192.38±54.02	158.31±59.06	0.355
Urea (mg/dL)		44.66±17.37	34.43±9.53	**0.003**
Creatinine (mg/dL)		1.26±1.48	0.90±0.41	**0.040**
Albumin (g/L)		33.91±6.04	35.79±5.71	0.506
ALT (IU/L)		24.37±13.16	23.19±18.58	**0.028**
AST (IU/L)		51.72±38.21	39.70±48.13	0.873
Total Bilirubin (mg/dL)		1.15±1.06	0.94±0.86	0.066
Direkt Bilirubin (mg/dL)		0.56±0.61	0.30±0.51	**0.005**
Sodium (mEq/L)		140.00±3.41	139.38±2.99	0.207
Potassium (mEq/L)		4.37±0.45	4.49±0.38	0.317
Calcium (mg/dL)		8.31±0.81	8.37±0.73	0.527
CRP (mg/L)		69.17±65.44	44.94±46.20	0.362
Lactate (mmol/L)		1.86±1.40	1.39±0.51	**<0.001**
Flow (L/min)		4.55±0.39	4.47±0.41	0.881
X-Clamp time (minutes)		84.36±31.77	85.01±32.41	0.852
Total perfusion time (minutes)		111.53±33.93	109.98±35.41	0.621
CABG, n (%)	**SingIe**	2 (3.3)	1 (1.7)	0.249
	Double	19 (31.7)	17 (28.3)	
	Triple	20 (33.3)	25 (41.7)	
	Quatruple	19 (31.7)	17 (28.3)	

Data are show as mean±standard deviation or n (%). ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRP=C reactive protein, CABG=coronary artery bypass graft

Table 3. Comparison of perioperative clinical outcomes of the patients

Variables	Normothermia (n=60)	Hypothermia (n=60)	P value
Need for Intracardiac defibrillation, n (%)	20 (33.3)	32 (53.3)	**0.027**
Positive inotropic requirement, n (%)	19 (31.7)	34 (56.7)	**0.006**
IABP requirement, n (%)	3 (5)	5 (8.3)	0.464
Erythrocyte suspension (Units)	1.38±1.20	1.33±1.24	0.818
Postoperative drainage (mL)	1110.00±308.74	1124.42±301.05	0.711
Extubation time (hours)	6.73±1.73	7.38±2.60	0.182
ICU stay time (hours)	31.26±7.95	33.25±8.48	0.628
Total hospital stay time (days)	8.28±2.59	8.10±2.54	0.743

Data are show as mean±standard deviation or n (%). IABP=intra-aortic balloon pump, ICU=intensive care unit

rate were lower after cross-clamping in the normothermia group.

Among the advantages of intraoperative normothermia is the significantly lower need for defibrillation. However, when evaluated with a holistic approach, we think that this advantage of normothermia compared to hypothermia should be evaluated in a different category. For this reason, the reversibility principle of cardioplegia solutions used for myocardial protection and arrest in cardiac surgery and the selection of appropriate cardioplegia solutions can be considered as a solution at this point. In a study conducted by Cakir *et al*. [11] on this subject, it was stated that in patients who underwent isolated CABG with CPB, myocardial damage was less in normothermic (above 34oC) cardioplegia than in deep hypothermic (18-28oC) cardioplegia. In other words, it may be more useful to prefer mild hypothermic or normothermic cardioplegia solutions for myocardial protection, regardless of CPB temperature, or to evaluate myocardial protection temperature separately.

Kaplan *et al*. [12] investigated patients who underwent surgery under normothermia and hypothermia (intraoperative body temperature <34°C- ≥28°C) in terms of postoperative differences. In their study, they found that aortic cross-clamping time, CPB time, awakening and extubation times, ICU and hospital stay, drainage, mean serum lactate levels, arrhythmia rates, infection status, renal failure, neurological complications, myocardial infarction, inotrope, transfusion requirements, and mortality rates were similar between groups and stated that cardiac surgery could be performed safely at the patient's temperature without active cooling [12]. Ziyaeifard *et al*. [13] compared the effects of hypothermia and normothermia on cognitive functions after CABG surgery in their study. As a result of the study, it was found that cognitive impairment was lower in patients who underwent normothermic CPB during hospitalization after CABG surgery compared to those who underwent hypothermic CPB [13]. In cases of atrioventricular (AV) septal defect repair, Amer *et al*. [14] compared normothermic and mild hypothermic (32°C- 35°C) CPB. In their study, they reported higher liver enzymes, more inotropic support, and longer intubation time in the mild hypothermic group in the postoperative period. As a result, they concluded that normothermia during CPB provides better global tissue perfusion than hypothermia in elective surgeries for the repair of AV defects [14].

Bianco *et al*. [15] compared normothermia versus mild hypothermia (32°C-35°C) in patients undergoing cardiac surgery. They reported that postoperative renal failure and ICU stay were higher in patients who received mild hypothermia during CPB, but there was no difference in long-term survival between the two groups [15]. Boodhwani *et al*. [16] reported that rewarming had negative effects on renal function in patients who received mild hypothermia after CABG and that this should be avoided. In contrast, our study showed that there were negative results in renal parameters in the normothermic group compared to hypothermia. We believe that these differences may be

due to rapid rewarming or the time interval during rewarming and the sudden increase in temperature.

In the study by Yuksel *et al*. [17], normothermic and mild hypothermic CPB were compared in myocardial revascularization in patients with left ventricular dysfunction. In their study, they evaluated patients who underwent surgery under mild hypothermia (32ºC) and normothermia (≥35ºC) in terms of defibrillation rates, other morbidity problems and mortality. As a result of their study, they stated that normothermia provided less defibrillation requirement after aortic cross-clamping in patients with left ventricular dysfunction, which could be interpreted as better myocardial protection. However, they also showed that normothermia did not have an advantageous effect on postoperative stroke, postoperative atrial fibrillation, renal failure, and mortality [17]. In parallel with this study, the need for defibrillation was less in the normothermia group in our study.

In a study, it was determined that cardiac index, systemic oxygen delivery, and consumption, duration of respiratory support, ICU, and hospital stay were similar in the postoperative period after normothermic and hypothermic CPB in patients undergoing combined valve surgery [18]. It has also been stated that hypothermic and normothermic CPB show similar clinical results in congenital and pediatric patients other than adult cardiac surgery [19]. In our study, the duration of respiratory support, ICU, and hospital stay were similar.

Regarding the stages of hypothermia, it is stated that mild hypothermia is more advantageous during CPB. It is stated that mild hypothermic CPB temperature provides better clinical results in terms of less inotropic support, less blood loss, less blood transfusion, better platelet count, shorter hospital stay, and less ventilation support compared to other hypothermic temperatures [2]. It is stated that moderate hypothermia (24°C) provides better protection of the intestinal barrier compared to deep hypothermia (18°C) during total circulatory arrest [20]. When the studies in the literature are examined, it is seen that normothermic and hypothermic CPB applications have different advantages over each other. In our study, we also concluded that the two methods have different advantages.

Limitations

The limitations of this study include the small number of cases undergoing normothermic cardiac bypass in the center where the study was conducted. In addition, the fact that only postoperative day 1 biochemical and blood gas parameters were taken into account in the evaluation is among the other limitations of the study. We believe that conducting similar studies in multicenters, with more patients and patient groups that have undergone different cardiac surgical operations will yield more comprehensive and general results.

CONCLUSION

In CABG surgery performed with CPB, the advantages of intraoperative hypothermia compared to intraoperative normothermia on the outcome are significantly lower levels of urea, creatinine, direct bilirubin, and lactate. The advantages of intraoperative normothermia are less defibrillation and inotropic requirements.

Ethical Statement

This study was approved with the protocol dated 31/10/2022 and numbered HRÜ/22.21.05 of the Harran University Clinical Research Ethics Committee.

Authors' Contribution

Study Conception: BA, ME; Study Design: BA, ME; Supervision: BA, ME, AKA, MA, SY; Funding: BA, ME, AKA, MA, SY; Materials: BA, ME, AKA, MA, SY; Data Collection and/or Processing: BA, ME, AKA, MA, SY; Statistical Analysis and/or Data Interpretation: BA, ME, AKA, MA, SY; Literature Review: BA, ME, AKA, MA, SY; Manuscript Preparation: BA, ME, AKA, MA, SY and Critical Review: BA, ME, AKA, MA, SY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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