Original Article

Fibrinogen and Fibrin Degradation Products' Levels in Cardiopulmonary Bypass with Mild-Hypothermia versus Normothermia

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Abstract

Background: Coagulation cascades are activated during Cardiopulmonary Bypass (CPB) and their proper monitoring and maintenance determine the outcomes of operation to a big extent. Here, we assessed serum fibrinogen and Fibrin Degradation Products (FDP) in adult patients undergoing CABG with using CPB, either with hypothermia or normothermia.

Materials and Methods: In a cross-sectional study, 80 adult patients' candidate for elective CABG were randomly assigned into two groups: hypothermia and normothermia to assess fibrinogen and FDP, perioperatively.

Results: Patients included 32 men (80%) in the hypothermia group and 26 men (60%) in the normothermia with the mean age of 61.43 ± 12.64 years. The mean temperature in the hypothermia group was 32.33 ± 1.44 and 35.33 ± 0.71 in the normothermic group. Differences in fibrinogen levels between the two groups were not significant (Fib before CPB, P=0.893, and Fib after declamping, P=0.057). The serum level of FDP before and during CPB was not significantly different in hypothermia and normothermia groups (P=0.412, P=0.778, respectively).

Conclusion: During cardiac surgery in hypothermia and normothermia conditions rate of fibrinogen decreased 25% after declamping in each group; this decrease seems to be due to hemodilution. FDP levels were similar in both groups.

Keywords: Fibrinogen, Fibrin Degradation Products, Hypothermia, Cardiopulmonary bypass

Please cite this article as: Ghasemzade B, Ghodrati M, Kachuian N, Banakar Y, Gorjipour F, Zarei AA, et al. Fibrinogen and Fibrin Degradation Products' Levels in Cardiopulmonary Bypass with Mild-Hypothermia versus Normothermia. J Cell Mol Anesth. 2020;5(3):157-63.

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Introduction

The cardiopulmonary system is related to homeostasis through an interconnected network of signaling pathways controlling its function and regulating the balance between inflammation and hemostasis (1-4). Hemolysis and fibrinolysis systems are affected by the beginning of the cardiopulmonary bypass (CPB), with the exposure of blood to the components of the circuit. This exposure results in the activation of clotting factors and immune cells and may trigger disturbances in bleeding and hemolysis disorder (5, 6). Fibrinogen,

as a fibrin precursor, is the focal factor inactivation of coagulation and has a dual role in platelet congregation and insoluble fibrin hematoma formation. According to recent records, decreasing plasma fibrinogen concentration can affect hematoma formation from 25 to 50 percent (7, 8). There are several mechanisms for decreasing the concentration or function of blood fibrinogen during heart surgery. These mechanisms include activation of the molecular effectors of coagulation pathways through tissue damage, exposure of cellular compartments and platelets to the non-self surfaces, CPB priming, deficit replacement with crystalloid and colloid, and transfusion of blood containing low fibrinogen and coagulation factors (9) which results in hemodilution and decrease in the concentration of fibrinogen, hematocrit, and albumin (10). Activation of platelets and coagulation factors in contact with CPB circuit and surgical trauma leads to their consumption. This trend is shown by evaluating Fibrin Degradation Products (FDP) D-dimer that indicates the consumption of fibrinogen. Besides, the excessive activation of the fibrinolysis pathway causes fibrinogen loss (11, 12). It is still unknown which mechanism leads to fibrinogen decrease during surgery. FDP is an important indicator of bleeding after thrombolysis treatment (13). Fibrinogen degradation and FDP have a direct effect on thrombosis formation (14, 15) and its high level is observed after CABG in the absence of aprotinin (16).

Since hypothermia can negatively affect the coagulopathy (17), we hypothesized that the hypothermia could affect the coagulation pathway activation in CABG patients with hypothermic and normothermic CPB, hence affecting the level of fibrinogen and Fibrin Degradation Products. The present study investigated the serum fibrinogen and the FDP changes as molecular markers of the coagulation in mild-hypothermia versus normothermia in patients undergoing CPB.

Methods

Patients: This was a cross-sectional study. The study population consisted of adult elective patients undergoing coronary artery bypass graft surgery (CABG). Sampling was done randomly. Eighty patients were assigned into two groups with the method of block randomization with the blocks of 4 patients: hypothermia group and normothermia group. Fibrinogen was measured in 40 patients of each group and FDP was measured in 22 patients of each group. The study was conducted in line with the criteria for the institutional research ethics committee of the Shiraz University of Medical Sciences (SUMS, Tehran, Iran) after filling an informed consent form (ethical code IR.SUMS.REC.1397.375). The study protocol was registered with the code IRCT20180930041189N1 at the Iranian Registry of Clinical Trials (IRCT) database.

Exclusion criteria were history of thrombosis; bleeding or any coagulation disorders, regular use of aspirin, congenital fibrinogen disorders, and drug abuse, and redo surgery. Data were gathered in four sections, demographic (age, sex, height, and weight), pre-operation, during operation, and post-operation.

Pre-operation data included medicines used, biochemistry markers, and hematology indexes. Perioperative data were duration of cardiopulmonary bypass, surgery, and cross-clamp, amount of hypothermia and normothermia level, and the number of packed cells and blood products required. Post-operative data were the amount of bleeding, and the number of packed cells and blood products used.

Procedures: CABG surgery was performed according to the standard protocol of the center for these patients. Anesthesia induction was done with 2 µg /kg sufentanil and 3 mg/kg sodium thiopental and 0.1 mg/kg Pancuronium for all patients and was maintained with 0.5-1% isoflurane. It was maintained with 0.1 mg/kg/h atracurium, 1- 2 µg/kg fentanyl, and 0.5- 1 µg/kg midazolam during cardiopulmonary bypass and all patients received 300 u/kg heparin before the bypass to make the activated coagulation time (ACT) over 480 seconds. Hypothermia management, has four levels: mild (32–35°C), moderate (28–32°C), severe (20–28°C), profound (<20 C). In the present study, two types of temperature controls were applied: mild-hypothermia (32- 35°C) and normothermia (>35°C). The temperature of the heater-cooler and blanket was set to 30°C in the hypothermic group and 35°C in the normothermic group. The thermometers connected to the reservoir venous return measured the temperature.

To prime, the oxygenator in both groups, crystalloid (2000 mL ringer) and colloid (50 mL albumin) were used. During CPB, heparin was prescribed to achieve the target ACT. At the end of CPB and disconnecting from the cardiopulmonary bypass system, protamine sulfate of 1 mg per 100 units of heparin was administered to achieve the target ACT of 80 to 120 seconds. Two mL of arterial blood samples were drawn from patients at two times and kept into tubes containing trisodium citrate. The first sample was taken before the injection of heparin and CPB start and the second one was taken before the beginning of the rewarming procedure in the hypothermic group and simultaneously with the aortic declamping in the normothermic group. Then, they were sent to the laboratory for testing fibrinogen and FDP. Clauss method was used to assay plasma fibrinogen according to the CDC and the CAP guidelines. FDP was measured using the human FDP ELISA kit (Production No: E-EL-H2194, Document number: ELAB-EK-WPRT5HF9, Company: Elabscience) in serologic assessments.

Statistical Analysis: Data were analyzed by Statistical Package for Social Sciences, version 14 (SPSS Inc., Chicago, IL, USA) on a Microsoft Windows-based setting. For studying correlations between variables, the Pearson test was used; if there were a normal data distribution pattern and Spearman in the absence of a normal distribution pattern. A paired t-test was used to compare a two-time normal variable. An independent t-test was used for variables with a normal distribution. A chi-square test was used for comparing frequencies of qualitative variables between groups. The level of significance was 0.05 and the power of analysis was 0.8.

Results

A cross-sectional study comprising 80 patients undergoing coronary artery bypass graft in two groups was conducted. The study population consisted of 22 female patients (27.5 %) and 58 male patients (72.5 %) with a mean age of (61.43±12.64) (29-82 years old). Demographic data, height, weight, and comorbidities,

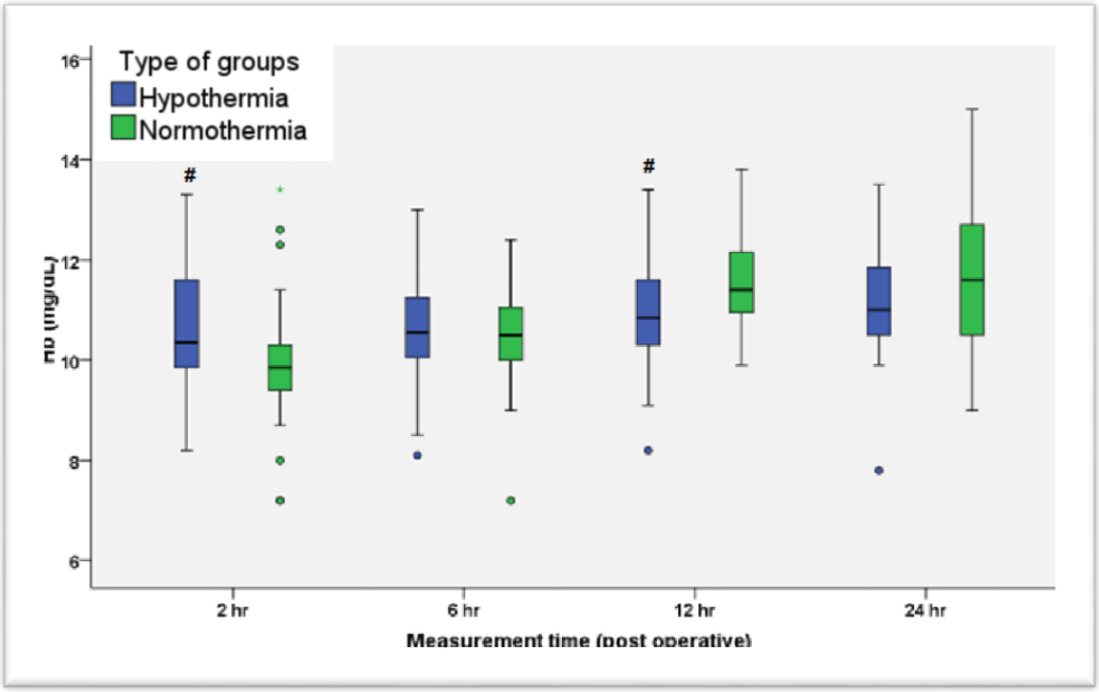

Figure 1. Changes Hemoglobin in 2, 6, 12, 24 hours after surgery. *P<0.05 compared with the Normothermia group at the same time.

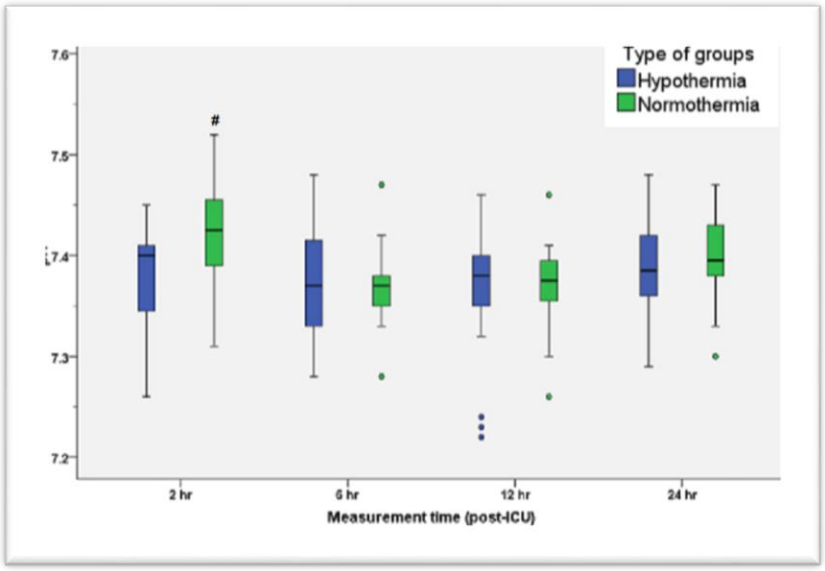

Figure 2. Changes in the pH at 2, 6, 12, and 24 hours after surgery. *P<0.05 compared with the hypothermia group at the same time.

Table 1: Patient Characteristics (N=80; allocated to two groups; 40 in each).

Variable	Normothermia Mean*±SD	Hypothermia Mean ± SD	P value
Sex			
Female (Numbers)	14	8	0.133
Men (Numbers)	26	32	
Age (y)	60.73 ±9.38	63.05±11.57	0.273
Weight (Kg)	72.93±9.51	70.05 ±12.46	0.290
Height (cm)	167.45 ±7.64	165.95 ±8.56	0.949
History			
MI (N)	2	3	
HLP (N)	15	22	
Smoker (N)	3	2	
Asthma (N)	1	2	>0.05
Hyperthyroidism (N)	1	1	
Digestive system disease (N)	2	0	

*Mean (range)
SD: Standard deviation
N: Number
MI: Myocardial ischemia
HLP: Hyperlipidemia
Y: years
Kg: Kilogram
cm: Centimeter

have shown in Table 1. There were no significant differences in the frequency of comorbidities between the two groups (P>0.05).

The mean temperature reduction in the hypothermia group was (3.96±1.42) and in the normothermia group was (1.03±0.72) (P≤0.001) (Table 2). While their mean body temperature at ICU entrance in the hypothermia group was (35.71±0.49) and in the normothermia group (36.07±0.50), respectively. There was no significant difference

Table 2: Intraoperative and postoperative variables of patients (N=80; allocated to two groups; 40 in each).

Variable	Normothermia Mean±SD	Hypothermia mean±SD	P Value
CPB Time (min)	58.65±8.51	59.98 ±10.26	0.401
Cross Clamp (min)	28.23±10.12	38.04 ±9.11	0.003*
Time for restoration of cardiac beating rhythm (s)	33.45±3.45	69.58 ±7.45	0.002*
Bleeding 24 h	645.12 ±203.27	652± 256.31	0.123
Hb (mg/dL) ICU	10.28± 1.06	10.46± 1.19	0.779
Hct (%) ICU	31.43± 2.61	30.48± 3.31	0.657
Temperature decrease in CPB (°C)	35.35± 0.71	32.33± 1.44	<0.001*

SD: Standard deviation,
CPB: cardiopulmonary bypass
min: minutes,
s: second,
h: hours
ICU: Intensive Care Unit
Hb: Hemoglobin
Hct: Hematocrit

between groups regarding measured outcomes (P=0.626).

However, time for restoration of cardiac beating rhythm after cross-clamp was lower in the normothermia group (P=0.002) (Table 2). Besides, cardiac rhythm in all patients was following normal sinus rhythm pattern, except two patients in the normothermia group demonstrating ventricular fibrillation.

The fibrinogen level between the two groups was not different. However, in each group's serum level of fibrinogen after declamping was decreased significantly compared with the before CPB time in both groups (P=0.001) (Table 3).

Comparing the FDP level between both groups revealed no significant difference at similar time points; also, the serum level of FDP before and during CPB was not significantly different in each group (P=0.412 and P=0.778, respectively) (Table 4).

The mean bleeding 24 hours after surgery is presented in table 2. There was no significant difference in both groups (P=0.717). The number of recipients of the packed cells was 40 (100%) in the hypothermia group and 34 (85%) in the normothermia group. Changes in blood Hemoglobin at 2, 6, 12, and 24 hours after surgery were not significant in both groups (P=0.779) (Figure 1).

Utilization of albumin, gelatin, and Hydroxyethyl starch) in ICU were not significantly different in both groups. Acidosis at 2 hours post-operation was significantly lower in the hypothermia group (P=0.002) (Figure2).

Table 3: Comparing fibrinogen level between both groups (N=80; allocated to two groups; 40 in each).

Variable	Normothermia Mean ± SD	Hypothermia Mean ± SD	P Value
Fibrinogen before CPB	326.23±95.65	357.05 ±114.72	0.893

Table 4: Comparing the FDP levels between two groups (N=80; allocated to 2 groups; 40 in each).

Variable	Normothermia Mean ± SD	Hypothermia Mean ± SD	P Value
FDP before CPB	26.42±33.37	21.84±23.49	0.136
FDP after declamping of aorta	24.02±25.40	22.35±24.89	0.492

FDP: Fibrin Degradation Product
One-way ANOVA: In normothermia P value:0.412 and in hypothermia P value= 0.778

Discussion

At the beginning of the CPB and the exposure of the blood to the CPB circuit as an exogenous entity, a complicated interaction starts between coagulation, fibrinolysis, and inflammatory systems (8, 10) leading to coagulation disorder, over-bleeding, and systematic inflammatory response syndrome due to activation of both cellular and humoral components (8). In the present study, the serum levels of fibrinogen and FDP were compared in the hypothermia and normothermia in patients under CABG surgery. Differences in the fibrinogen and FDP level between the two groups were not significant before. The serum fibrinogen decreased by 25% after declamping in both groups. It seems this reduction is highly influenced by hemodilution, while the serum FDP changes were not observed in both groups.

The mean consumption of packed cells was similar in both groups, wherein the hypothermia group all patients required transfusion, but only 24 cases were so in the normothermia group. It should be noted that the mean volume of bleeding in the first 24-hour after the surgery did not differ much but normothermic patients showed higher levels of Hemoglobin and Hematocrit.

A study conducted in Italy by Solomon et al. in 2014 revealed that fibrinogen measurement before and after CPB helps in the timely intervention for proper hemostasis and prevention of bleeding (18).

In a study by Kaplan et al. in 2018, patients were examined in two groups: hypothermia and normothermia. Aortic cross-clamp time, bypass time, waking and extubation time, duration of ICU and hospitalization, drainage, mean serum lactate level, arrhythmia, infection, renal failure, neurological complications, myocardial infarction, or mortality were the same in the two groups. Inotropic score and blood transfusion rates were significantly lower in the normothermic group than in the hypothermic group. They claimed that surgery is possible at the patient's normal body temperature and the risk from the lowering of the body temperature could be abstained (19). The results of the present study are in line with that except in the following items, lower acidosis in the hypothermic group, a significant rise of BUN in both groups, similar consumption of inotrope in both cases, and the shorter heart rhythm resuming meantime after the aortic decamping in the normothermic group.

According to a retrospective study by Williams et al. in 2018, patients were examined based on their body temperature, pH disorders, and amount of blood transfusion. There was no relation between hypothermia at the end of the surgery and the amount of blood transfusion after that. However, pH disorders were associated with an increase in transfusion after surgery (20). The present study confirms these findings although we could not find a meaningful relation between pH disorder and transfusion increase which might be due to the low sample size.

A study by Gielen et al. in 2015 compared the concentration of hematocrit, albumin, fibrinogen, and Fibrin Degradation Products (D-dimer, FDP) in 10 patients before and after CPB. The results showed that the concentration of plasma fibrinogen reduced by 30% during the surgery.

This decrease appears to be due to hemodilution. There was also a reduction in hematocrit and albumin and no significant elevation in D-dimer and FDP (21). The present study showed a 25 percent decrease in fibrinogen level and an increase in FDP in the hypothermic group.

A German study by Boldt et al. in 1996 on platelet function and coagulation system in CPB patients demonstrated that in two groups of patients undergoing hypothermic and normothermic CPB operations, hypothermia leads to more reduction in platelet aggregation and coagulation in hypothermic patients compared to normothermic ones (22).

Conclusion

Fibrinogen and FDP levels were similar in both groups when measured and compared at identical times. Post-declamping fibrinogen levels decreased in both groups compared to the preoperative values in the same group. It seems that this trend is a result of the physiologic and pathophysiologic effects of hemodilution; though more widespread research; both basic and clinical are needed to approve the latter assumption. However, from the clinical perspective, normothermic CPB appears to be associated with faster restoration of the heart rhythm

and shorter time for the cross-clamp throughout the procedure.

Acknowledgment

The authors thank the perfection team of Central Hospital in Shiraz, especially Mr, Yadollah Banakar for the full support in the center investigations.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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