

Effect of Temperature Changing during Cardiopulmonary Bypass on Coagulation in Patient Undergoing Coronary Bypass Graft: an Observational Pilot Study

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Background: Hypothermia and cardiopulmonary bypass (CPB) are the main factors that disturbed the coagulation process during cardiac surgery. Rotational thromboelastometry (ROTEM) can be used to monitor the coagulation changing from moderate hypothermia during coronary artery bypass graft (CABG) surgery.

Objective: The purpose of this study was to assess the effect of induced hypothermia on standard coagulation test and ROTEM to detect hemostasis changes in elective CABG.

Method: An observational pilot study was conducted on five patients. Blood samples were collected from the arterial line at six different time points: at baseline (after arterial cannulation), 5 minutes after heparinization, 10 minutes after CPB, when the rectal temperature reaching 32°C, and 10 minutes after protamine administration. The patient's serum was analyzed in ROTEM including INTEM, EXTEM, HEPTM, FIBTEM, and standard coagulation test.

Results: Our data showed prolongation of the coagulation time, clot formation time, and attenuation in alpha angle, A10 and maximum clot firmness (MCF) by INTEM, EXTEM, HEPTM, and FIBTEM from ROTEM during hypothermia during cardiopulmonary bypass. The standard coagulation test showed a decrease in platelet counts. However, the decrease of platelet counts did not lead to a decrease in the hemostatic function of platelets, as assessed by MCF.

Conclusion: No statistically significant differences between ROTEM and standard coagulation test from the effect of temperature change to moderate hypothermia (at 32°C) during CPB in CABG surgical patient.

Keywords: cardiopulmonary bypass, coagulation, coronary artery bypass graft, rotational thromboelastometry

Introduction

Excessive bleeding is a major and common complication of cardiopulmonary bypass (CPB) with hypothermia during open-heart surgery. Reoperation due to postoperative bleeding is a predominant complication and was associated with a significantly impaired prognosis.¹ The incidence of reoperation in Songklanagarind hospital has been reported as 3.52% in 2014-2015. The coagulopathy during cardiac surgery resulted from many mechanisms such as a combination of hyperfibrinolysis, platelet dysfunction, and reduced clotting factor levels caused primarily by the contact of blood with the CPB circuit and synthetic grafts, CPB related hemodilution, hypothermia, surgical trauma, heparin excess, and inadequate heparin reversal.^{2,3}

Hypothermia during CPB is generally applied to protect vital organs such as the brain, kidneys, lungs, and heart from ischemic injury during cardiopulmonary bypass by reducing the body's metabolic rate and decreasing oxygen consumption. However, hypothermic perfusion also has disadvantages that can contribute towards increased intra-operative and postoperative blood loss and increased rate of re-operation for bleeding.⁴⁻⁶ Platelet dysfunction, reduced coagulation factor activity, and induction of fibrinolysis also played important roles in these coagulopathic changes. However, platelet dysfunction and impaired enzymatic activity of coagulation factors can be reversible after the normalization of body temperature.

To identify the causes of coagulopathy, clinicians currently rely on conventional laboratory tests that have long turnaround times and cannot detect important coagulation defects

such as excessive fibrinolysis, platelet dysfunction, or specific coagulation factor deficiencies.^{3,7,8} As a result, clinicians frequently delay the therapy until the test results become available or resort to empiric therapy based on their clinical judgment. In this context, early and specific diagnosis and effective and targeted therapy of the underlying hemostatic pathology are of high clinical relevance.⁹

A point-of-care test, rotational thromboelastometry (ROTEM), is increasing frequently used not only because of its ease of use and rapid results, but also it can monitor multiple coagulation parameters.^{10,11} The commonly used ROTEM variables include coagulation time (CT; seconds), clot formation time (CFT; seconds), α -angle (degrees), the amplitude at 10 minutes after CT (A_{10} ; millimeters), maximum clot firmness (MCF; millimeters), and maximum lysis (ML; percent decrease in amplitude 60 min after MCF). CT represents the onset of coagulation, whereas the clot formation time and α -angle represent the initial rate of fibrin polymerization. MCF is a measurement of the maximal viscoelastic strength of the clot. An ML > 15% is used for the diagnosis of a premature breakdown of the clot (hyperfibrinolysis). Extrinsic rotational thromboelastometry (EXTEM) and intrinsic rotational thromboelastometry (INTEM) can be used in conjunction to diagnose specific coagulation problems. Fibrinogen rotational thromboelastometry (FIBTEM) is a modified EXTEM test with cytochalasin D, which inhibits platelet cytoskeletal reorganization and, thus, fibrinogen binding to platelet GP IIb/IIIa. By combining EXTEM and FIBTEM, the differential diagnosis of thrombocytopenia and/or hypofibrinogenemia is feasible. APTTEM is also a

modified EXTEM, in which aprotinin inhibits plasmin in vitro if systemic fibrinolysis was present. HEPTM contains heparinase in addition to the INTEM reagent. It is used as a pair with INTEM for the diagnosis of systemic heparin activity.

The aim of our study is to find the effect of temperature change during cardiopulmonary bypass on coagulation in patients undergoing coronary bypass graft surgery.

Methods

This observational study was approved by the Ethic Committee, Faculty of Medicine, Prince of Songkla University (REC. 58-031-08-1). All five patients gave their informed consent after receiving written information of the study. Patients were considered eligible if they were aged between 18-70 years undergoing CABG surgery with CPB, ejection fraction more than 40%. Exclusion criteria were as follows; emergency surgery, combined CABG with valve surgery, symptoms of chest pain within one month, congestive heart failure, use of warfarin or clopidogrel until the day of operation, history of coagulation disorder, fever (body temperature more than 38°C) and preoperative intra-aortic balloon pump insertion.

Anesthesia was induced with midazolam, fentanyl, propofol and then continued with sevoflurane to maintain anesthetic depth. Muscle relaxation was achieved with rocuronium. All patients received cefazolin as antibiotic prophylaxis. In all patients, tranexamic acid was administered at the dose of 10 mg/kg before the surgical incision then infusion at rate of 1 mg/kg/hr. The CPB circuit was primed with normal

saline solution, 1 mg/kg of heparin and 0.3-0.4 g/kg of mannitol. Patients received heparin 3-4 mg/kg intravenous to achieving the kaolin-activated activated clotting time more than 400 seconds before undergoing complete CPB with the standardized continuous non-pulsatile flow of 2.2 to 2.4 L/min/m². Myocardial protection was performed by the induction of electromechanical arrest with cold cardioplegia enriched with potassium chloride and magnesium sulfate. Heparinization was maintained during the whole CPB period with the coagulation time above 400 seconds. All surgical patients were operated on the same team of surgeons, anesthesiologists, and perfusionists.

Blood samples

Blood samples were drawn from an arterial catheter connected to the flush system containing 0.9% sodium chloride solution. The first 5 ml of each blood sample was discarded to eliminate the dilution effect of saline. Blood samples were obtained at six time periods: baseline (after arterial cannulation) (T₁), 5 minutes after heparinization (T₂), 10 minutes after on CPB (T₃), when rectal temperature reaching 32°C (T₄), 30 minutes after rectal temperature at 32 ± 0.5°C (T₅) and 10 minutes after protamine administration (T₆). Blood samples were kept in a tube containing citrate and were immediately sent to the Central Laboratory for ROTEM and conventional coagulation tests. ROTEM included INTEM, EXTEM, HEPTM, FIBTEM and APTM. Normal ranges are summarized in appendix A.12 The conventional coagulation tests included hemoglobin, hematocrit, platelets count, prothrombin time (PT), thromboplastin time

(PTT), international normalized ratio (INR), and fibrinogen.

Statistical analysis

Statistical analysis was performed using the R 2.11.1 software with Epicalc package. For descriptive statistics, means and standard deviations (SD) was used for normal distribution and continuous data, while the frequency with percentage was used for categorical data. In terms of analytic statistics, for all determinations, *P* values of < 0.05 were considered to be statistically significant.

Results

A total of five patients undergoing CABG surgery with CPB circuit between July 2015 and December 2015 were analyzed. Three patients (60%) were male and two patients (40%) were female. The mean (SD) body weight was 60.3

Table 1 Patient's characteristics

Variables	All patients (n=5)
Age, year	55.6 + 8.68
BMI, kg/m ²	24.1 + 3.73
Preoperative EF, %	62.6 + 15.7
Aortic cross-clamp time, minutes	91.8 + 17.3
Cardiopulmonary bypass time, minutes	126.2 + 17.5
Operation time, hour	4.49 + 0.5

Data are presented as mean (SD).

BMI: body mass index; EF: ejection fraction.

(5.85) kg, height 158.8 (9.6) cm. Hypertension was the underlying disease in three patients (60%). Two patients (40%) had dyslipidemia and one patient had both diabetes mellitus and cerebrovascular disease. One patient died from sepsis and multiorgan failure at 6 days postoperatively. Patient characteristics are summarized in table 1.

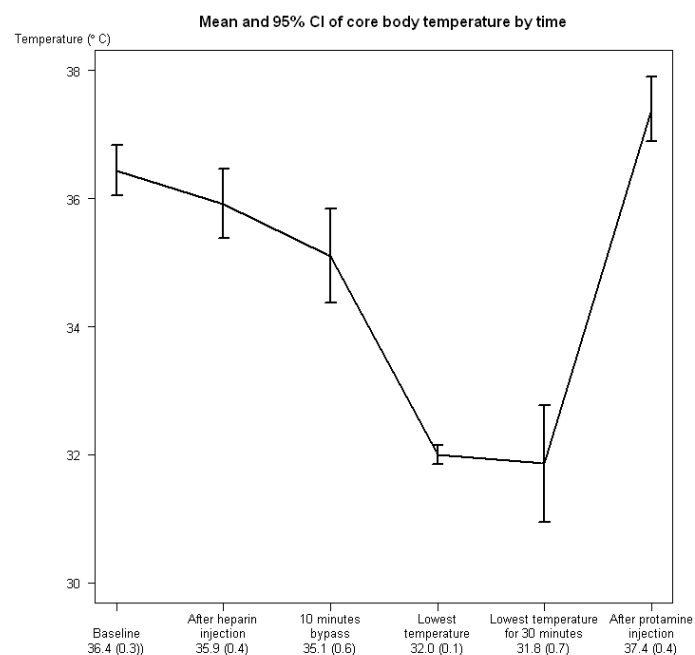


Figure 1 Mean body core temperature change for all five patients at the times indicated

The temperature of the patients in this study ranges from 31.9 -37.4°C. Induced hypothermia at 32°C was achieved during the CPB time in all patients. Figure 1 shows the changes in the mean (SD) rectal temperature over the surgical period.

The results of perioperative conventional coagulation tests are shown in table 2. The mean

fibrinogen levels at 10 minutes after protamine administration decreased from baseline but it was not statistically significant ($p = 0.14$).

Whenever the patient's body temperature was less than 37°C, the prolongation of the CT, CFT, and the decrease of alpha angle, A10, and MCF were detected (Table 3).

Table 2 Conventional coagulation data at baseline (T_1), 5 minutes after heparinization (T_2), 10 minutes after on CPB (T_3), at rectal temperature 32°C (T_4), 30 minutes after rectal temperature at $32 \pm 0.5^\circ\text{C}$ (T_5) and 10 minutes after protamine (T_6)

Parameter	T_1	T_2	T_3	T_4	T_5	T_6
ACT, sec	133.2 (18.6)	593.6 (81.5)*	549.0 (141.7)*,†	746.8 (430.5)*	568.0 (69.7)*	133.8 (17.7)
Hb, g/dL	13.1 (1.33)	12.4 (1.26)	8.54 (0.82)*,†	8.48 (1.31) *	8.02 (1.49) *	9.26 (1.52) *
Hct, %	40.0 (3.24)	38.2 (3.99)	26.3 (2.35)*,†	25.7 (4.03) *	24.6 (4.41) *	28.2 (5.05) *
Platelets, x10 ⁹ /L	211.8 (56.0)	212 (52.0)	156.2 (52.6)	140.8 (52.7)	149.8 (59.4)	133.4 (49.3)
PT, sec	12.4 (0.58)	> 100*	> 100*	> 100*	> 100*	21.3 (5.63) *
PTT, sec	25.2 (1.52)	> 190*	> 190*	> 190*	> 190*	30.0 (7.85) *
INR	1.07 (0.05)	NA	NA	NA	NA	1.64 (0.11) *
Fibrinogen, mg%	684.2 (292.5)	NA	NA	NA	NA	434.8 (123.5)

Data are presented as mean (SD). min: minute; sec: second; ACT: activated clotting time; Hb: hemoglobin; Hct: hematocrit; PT: prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio; NA: not applicable.

* Significantly different from baseline. † Significantly different from heparin injection.

Table 3 Rotational thromboelastometry values for INTEM and HEPTM at baseline (T_1), 5 minutes after heparinization (T_2), 10 minutes after on CPB (T_3), at rectal temperature 32°C (T_4), 30 minutes after rectal temperature at $32 \pm 0.5^\circ\text{C}$ (T_5) and 10 minutes after protamine (T_6)

ROTEM test	INTEM T_1	HEPTM T_1	HEPTM T_2	HEPTM T_3	HEPTM T_4	HEPTM T_5	HEPTM T_6	INTEM T_6
CT	173.6 (31.5)	160.4 (34.8)	275.6 (86.8)*	235.8 (76.9)	182.4 (29.2)	207.5 (37.4)	200.2 (32.8)	194.6 (18.8)
CFT	62.2 (13.1)	66.8 (17.9)	108.6 (40.1)	107.2 (51.8)	107.4 (34.6)	103.5 (31.4)	102.6 (34.1)	110.0 (46.0)
α	77.8 (2.6)	77.2 (3.8)	68.8 (7.3)	71.2 (6.9)	71.4 (4.8)	73.2 (5.1)	70.8 (5.7)	72.0 (6.4)
A ₁₀	58.8 (7.2)	55.4 (7.1)	53.0 (7.8)	48.4 (8.3)	46.0 (8.0)	46.5 (7.3)	46.4 (7.7)	47.0 (7.5)†
MCF	64.6 (6.0)	61.4 (6.1)	61.0 (6.3)	57.4 (6.8)	54.6 (7.1)	54.8 (5.3)	55.0 (6.8)	56.0 (7.0)

Data are presented as mean (SD). CT: clotting time; CFT: clot formation time; α : alpha angle; A10: clot amplitude at 10 minutes; MCF: maximum clot firmness

† Significantly different from INTEM at baseline (T_1), * Significantly different from HEPTM at baseline (T_1)

There was no difference between INTEM and HEPTM for any of the parameters at baseline (T_1). ROTEM parameters at baseline were within normal ranges for all patients. At T_2 or 5 minutes after heparin administration compared to the EXTEM and HEPTM test at T_1 , CT in EXTEM was prolonged by 43 seconds and CT in HEPTM was prolonged by 115.2 seconds. Both of them were significantly different from baseline ($p = 0.006$, power 96% and $p = 0.038$, power 79% respectively) (Table 3 and 4). CT in FIBTEM was statistical significantly prolonged by 57.1 seconds ($p = 0.011$, power 97%) (Table 4). At T_3 (10 minutes after on CPB) compared with T_2 , CT in EXTEM and HEPTM were reduced by 28.2 mm, 39.8 mm respectively. At T_4 (rectal temperature 32°C) and T_5 (after maintenance rectal temperature at $32 \pm 0.5^\circ\text{C}$ for 30 minutes), CT in EXTEM increased when

compared with T_3 . There were no statistically significant. At T_6 after heparin reversal, CT in INTEM and HEPTM were comparable to those at T_5 .

Clot formation time was compatible with clotting time. There was statistical significantly prolong between those at T_1 and at T_4 in EXTEM ($p = 0.033$, power 74%) (Table 4).

A_{10} had a statistically significant decrease between at T_1 and at T_4 , T_5 in EXTEM ($P = 0.041$, power 68% and $p = 0.045$, power 57% respectively) (Table 4).

MCF which reflects maximal clot strength, was not affected by temperature changes from 31.9°C to 37.4°C in EXTEM, HEPTM, and FIBTEM (Table 3, 4). However, MCF in EXTEM and HEPTM demonstrated to decrease when the thromboelastograph was run at temperature less than 37°C

Table 4 Rotational thromboelastometry values for EXTEM and FIBTEM at baseline (T_1), 5 minutes after heparinization (T_2), 10 minutes after on CPB (T_3), at rectal temperature 32°C (T_4), 30 minutes after maintenance rectal temperature at $32 \pm 0.5^\circ\text{C}$ (T_5) and 10 minutes after protamine (T_6).

	T_1	T_2	T_3	T_4	T_5	T_6
EXTEM						
CT	45.0 (18.8)	88.0 (17.7)*	60.2 (11.5)	62.2 (7.4)	67.8 (8.8)	64.0 (9.5)
CFT	70.0 (22.8)	70.6 (13.7)	100.4 (32.7)	113.8 (29.7)*	111.6 (37.8)	109.8 (38.6)
α	76.8 (4.6)	76.8 (2.8)	72.4 (5.9)	70.6 (4.1)	70.6 (5.1)	69.0 (7.0)
A_{10}	61.6 (8.3)	58.4 (5.6)	51.0 (8.7)	48.4 (8.7)*	49.0 (8.4)*	49.8 (9.9)
MCF	68.2 (6.1)	66.2 (4.6)	61.0 (7.1)	58.4 (7.5)	58.6 (6.5)*	59.2 (8.7)
FIBTEM						
A_{10}	21.4(9.1)	18.0(5.6)	13.8(4.5)	13.2(4.1)	11.6(2.6)	12.6(3.4)
MCF	23.0(9.4)	19.5(5.8)	15.4(5.5)	15.0(4.7)	12.8(3.1)	13.4(3.9)

Data are presented as mean (SD). CT: clotting time; CFT: clot formation time; α : alpha angle; A_{10} : clot amplitude at 10 minutes; MCF: maximum clot firmness.

* Significantly different from baseline (T_1). $P < 0.05$.

and increase when patients were rewarmed to normothermia. Additionally, MCF in FIBTEM that decreased during hypothermia and dropped to the lowest at CPB 32°C for 30 minutes but raised again to within normal range (9-25 mm) and significantly increase after rewarming to normothermia.

Discussion

The effect of hypothermia on coagulation in patients undergoing CABG with CPB circuit could be determined by assessment of standard coagulation tests and ROTEM during active cooling to 32°C body core temperature. We found no significant correlation between temperature and blood coagulation but hypothermia leading to an impairment of the coagulation variables.

After induction of CPB, the platelet count decreased with a decrease in hematocrit, so, the dilution of platelet count by the priming fluids seemed to be likely. After induction to moderate hypothermia at 32°C, our data showed a minor decrease of platelet count at temperature 32°C from baseline without the decrease of hematocrit. Low temperature at 32°C had an influence to decrease platelet count as same as in the previous studies.^{13,14} However, this decrease in platelet count was not clinically significantly different from baseline and was still within the normal range. Furthermore, this reduction of platelet count did not lead to the decrease in the hemostatic function of platelets, as assessed by MCF in ROTEM.

PT, PTT, and INR were prolonged from heparin effect. However, the fibrinogen level returned to normal range after rewarming the body core temperature to normothermia.

Therefore, it was in the same manner as ACT which was prolonged from heparin influence and it also returned to normal after reversal of anticoagulation effect with protamine administration. The dose of 1 mg of protamine per 100 units of heparin was used in this study and ACT value after separation from CPB was close to the baseline value.

The use of high dose of heparin during CPB should affect ROTEM parameters. Gronchi et al.^{1,15} explained the HEPTM measurements were valid in the presence of very high heparin concentration and the EXTEM reagent is stable in the presence of heparin concentration above 5 UI ml⁻¹. Although the heparin concentration was unknown during CPB, the authors assumed that all of EXTEM variables in this study were within the normal range at heparin doses 4-5 mg/kg. Both HEPTM and EXTEM can be used to evaluate hemostasis during CPB.

ROTEM variables: clotting time (CT) represents the initiation of clotting is mainly on coagulation factor activity, whereas clot formation time (CFT) and alpha angle (α) represents the formation rate of the clot depend on plasma coagulation and the interaction of platelets with fibrin. Maximum clot firmness (MCF) reflects maximal clot strength, in our study, the decrease of temperature from 37.4°C to 31.9°C did not affect MCF in EXTEM, HEPTM, and FIBTEM. However, MCF in EXTEM and MCF in HEPTM demonstrated to decrease when the thromboelastograph was run at the temperature less than 37°C and increased after rewarming the patients to normothermia. As same as MCF, FIBTEM decreased during hypothermia and reached the lowest at CPB 32°C for 30 minutes but within the normal range (9-25 mm) and

significantly increase after rewarming to normothermia. Finally, our data showed prolonged in CT and CFT in EXTEM, INTEM, HEPTM and slightly decreased in α , A_{10} , and MCF. The same as in the previous trial of TEG data¹³, these finding indicates the decrease in the initiation and speed of clot formation but not the deterioration in clot quality.

The previous report suggested that the threshold levels of A10 and MCF on FIBTEM values during the CPB were 8 and 9 mm, respectively, for predicting the fibrinogen concentration less than 150 mg/dl after CPB.¹⁶ Our present results showed that the A_{10} and MCF in FIBTEM during CPB decreased from baseline but these values were higher than threshold levels, although fibrinogen level could not be evaluated during CPB. We can predict the fibrinogen concentration in our study that it was more than 150 mg/dl. None of the five patients required cryoprecipitate transfusion postoperatively. Additionally, A10 and MCF in FIBTEM in this study were well correlated with fibrinogen concentration both at baseline and after protamine administration. However, there is currently no consensus on the threshold of hypofibrinogenemia for transfusion decisions in cardiac surgery.

In this study, all patients received tranexamic acid as an antifibrinolytic after baseline measurement. This is the routine management in our hospital because the administration of antifibrinolytic drugs in cardiac surgery is class I (A) recommendation.¹⁷ We did not observe increase fibrinolysis, which may be explained by the routine use of a prophylactic antifibrinolytic agent. Therefore, the measurement of clot lysis in APTM might be disturbed.

Although, there were differences of the ROTEM results between the time point of blood sampling, they remained within normal limit. None of them were clinically relevant. It was demonstrated that ROTEM is a highly sensitive tool for detecting subclinical changes in hemostatic mechanism.

The limitation of this study is the small number of patients because of the pilot study. Any differences in ROTEM and standard laboratory test require larger adequately powered study. Secondly, platelet dysfunction during cardiac surgery cannot be detected by ROTEM test, performing platelet function tests in addition to ROTEM test would be helpful.

Conclusion

In conclusion, our current findings showed no statistically significant ROTEM results of the temperature changing during cardiopulmonary bypass in the patient undergoing coronary bypass graft. The standard coagulation test at hypothermia at 32°C showed the decrease of platelet count but did not lead to hemostatic dysfunction of platelets, as assessed by MCF in ROTEM. The sample size in this study was not adequate to confirm that ROTEM can not predict the coagulopathic effect. Therefore, further studies are required to confirm this.

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Conflict of interest

All authors have no conflict of interest to report.

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APPENDIX

APPENDIX A Normal reference values of ROTEM assays¹²

	CT (sec.)	CFT (sec.)	Alpha angel (degree)	A10 (mm.)	MCF	ML (% of MCF)
INTEM	100-240	30-110	70-83	44-66	50-72	< 15
EXTEM	38-79	34-159	63-83	43-65	50-72	< 15
FIBTEM	MCF < 9 mm: reduced fibrinogen level or impaired polymerization Therapy: infusion of fibrinogen (or larger quantities of FFP) MCF > 25 mm: increased fibrinogen level. This may lead to normal clot formation in EXTEM or INTEM in spite of thrombocytopenia					
HEPTEM	A significant shortened CT in HEPTEM as compared to INTEM is indicative to a heparin effect					
APTEM	An improved clotting (shortening of CFT, higher MCF) in APTEM as compared to EXTEM is a sign for fibrinolysis					

CT: clotting time; CFT: clot formation time; A₁₀: clot amplitude at 10 minutes after CT; MCF: maximum clot firmness; ML: maximum lysis; FFP: fresh frozen plasma.