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The effect of temperature and hemodilution on activated clotting time during coronary artery bypass grafting

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Abstract

Activated clotting time (ACT) is an important test to measure the anticoagulation in cardiac surgeries. In this study different factors were examined which affect ACT during Coronary Artery Bypass Grafting (CABG). Blood Samples from 21 patients were taken and examined by using ACTALYKE MINI II. Once CPB initiated, the effect of hemodilution was measured on pre-CPB ACT value ($P<0.05$). Hemodilution occurred at the start of CPB caused a prolongation of ACT. After aorta was cross clamped, patient was cooled moderately to 32±2˚C. The ACT value increased in the result ($P<0.05$) which proved significant. This change was due to low metabolic rate and decreased function of enzymes. Before termination patient was rewarmed to normothermia 36±1˚C. This increase in temperature caused a decrease in ACT value ($P<0.05$). This change occurred due to an increase in metabolic rate and functioning of clotting enzymes, also there was a decrease in the blood volume due to urination. These findings can be used for better management of anticoagulation during CPB. So, ACT value has a direct relationship with hemodilution and inverse relationship with temperature.

Introduction

Exposure of blood to artificial surfaces during cardiopulmonary bypass (CPB) activates the blood platelets, and coagulation system, results in excessive thrombus formation [1]. The systematic administration of heparin prior to the induction of CPB and the neutralization of heparin by protamine sulfate at the end of CPB are essential for performing cardiac surgery. During CPB, large doses of heparin are used to prevent both thrombosis in the patient and coagulation in the pump oxygenator. Activated clotting time (ACT) has been recommended as a method both for determining heparin function and for indicating the amount of protamine sulfate required for heparin neutralization [2].

ACT is a popular method for assessing patient response to heparin because of its reliability, simplicity and sensitivity [3] and can be carried out quickly and easily with stable reagents in the operating room and ICU. ACT vial contains Celite or Kaolin as a contact activator of the intrinsic pathway of the coagulation system. The increase in ACT in the heparinized patient is directly proportional to the concentration of heparin in the blood. ACT is not measurement of heparin concentration, but it measures heparin function and is influenced by medication, hyperthermia, hypothermia etc. [4, 5].

Bull *et al* recommended a therapeutic range of ACT during the CPB from 300 to 600 seconds, so that no blood clots occur in the extracorporeal circuit when the ACT is greater than 300 seconds. The lower limit is based on clinical observation [6].

Coagulation is affected by numerous variables, including physical and biological processes. Patients undergoing hypothermic CPB are more likely to have increased intra- and postoperative blood loss and a higher rate of reopening due to bleeding [7, 8]. Mild hypothermia (34 ° C) is the critical point at which reduced blood clotting and a significant change in platelet activity are observed [9]. In addition, hemodilution induces marked anticoagulation that is not induced by heparin, due to which the dilution of clotting factors and platelets [10].

It has been shown that in addition to the heparin concentration, several factors also influence the ACT. This study is designed to quantify the effects of hemodilution and temperature on ACT during CPB in CABG. There are many factors like hypothermia and hemodilution which contributes in hemostasis [11]. If we consider these factors, we can manage anticoagulation during CPB more efficiently with or without additional dose of heparin and also, we can eliminate chances of accidents [12].

Materials and Methods

Inclusion and exclusion criteria

The study was carried out on patients undergoing coronary artery bypass grafting surgery at Faisalabad Institute of Cardiology, Faisalabad. Only adult male Patients who had body weight between 60kg to 85 kg were subjected for study. Operations which required any additional dose of heparin, extra prime solution or homologous blood infusion were excluded. Redo-operations and emergency bypass were also excluded.

Sampling

21 Patients undergoing coronary artery bypass grafting surgery were subject of interests in the study. Non-probability convenient sampling method was used to collect the data. The Patients included in this study were treated with mild hypothermia (31°C to 33°C) as per the surgeon's recommendations. The induction was done following anesthesia protocols and the patient's body surface area (BSA) weight. Atracurium was given to facilitate tracheal intubation. The maintenance of anesthesia was done by giving intravenous and inhalational anesthesia. The CPB was established using heart lung machines Terumo System 1 and Terumo System 8000. The hard-shell membrane reservoirs used were Maquet Quadrox Adult and Medtronic Affinity Fusion. The sites of cannulation used for the arterial cannulation was ascending aorta and the size of the cannula was given according to the flow rate and BSA calculated from Dubois formula. The venous cannulation was done by using double stage cannula in right atrium for CABG cases according to the patients flow rate. The cannulation for cardioplegia was done by the antegrade route or retrograde. The Extracorporeal circulation circuit was primed using the Lactated ringer solution 1200 ml as a priming solution, 25 ml sodium bicarbonate, 2.0 ml (10,000units) of sodium heparin injection (5000 I.U/ml) and 25 ml Mannitol (**Table 1**).

Table 1: Composition of Prime solutions

	Prime Solution		
Ringer lactate	1200 ml	Steroids	Nil
Sodium Bicarbonate	25 ml	Calcium	Nil
Mannitol	23 ml	Blood	Nil
Heparin	2ml (10,000units)		

Anticoagulation was established with a dose of 300-400 USP units/kg heparin sodium injection (5000 I.U/ml), injected in the central venous line of a patient five minutes before the initiation of CPB to achieve ACT value >480 seconds. The perfusion flows were targeted according to flow calculated from BSA and the mean arterial pressure was greater than 60 mmHg and less than 80 mmHg. Perfusion flow along with gas flow was maintained in such an order to maintain arterial oxygen tension greater than 150mmHg and arterial carbon dioxide tension between 30 to 40 mmHg. The Actalyke Mini II was used with C-ACT Tubes containing celite to measure the ACT of the patient at the times mentioned in Table 2. Afterwards blood sample was added to the tube and slightly shook to mix with the blood and then inserted in the port of machine. The ACT vial rotated and heated simultaneously by Actalyke Mini II and gave-us the value of activated clotting time. All the readings noted precisely. Activated clotting time of blood samples drawn simultaneously from a well-flushed port at the following times as shown in **Table 2**.

Table 2: Time intervals of samples for ACT readings

Sample name	Time to take sample
Baseline sample	Prior to any major surgical trauma and heparin administration
Prior to CPB	Five minutes following heparin administration
On CPB sample	Five minutes after initiation of bypass and prior to the induction of hypothermia; to measure the effect of Hemodilution
During mild hypothermia	To measure the effect of a decreased temperature at 32˚C
Once rewarmed	To measure the effect of a return to normothermia at 36.5˚C
After termination	To measure after protamine administration

Statistical Analysis

The pair 1 result shows that Baseline ACT value has significant (P-value≤0.05) relation with pre-CPB ACT value due to heparinization. The pair 2 result shows that pre-CPB ACT value has significant (P-value≤0.05) relation with hemodilution ACT value due to Prime hemodilution. The pair 3 result shows that hemodilution ACT value has significant (P-value≤0.05) relation with hypothermia ACT value due to decrease in temperature. The pair 4 result shows that hypothermia ACT value has significant (P-value≤0.05) relation with normothermia ACT value due to increase in temperature.

Central tendencies of ACT values

The data was analyzed by using SPSS version 26.0. Continuous variables were reported as mean ± standard deviation and compared by using the paired-sample T-Test. All P-values were ≤ 0.05, considered as significant. All tests were proved significant as the P-value of the test is smaller than 0.05.

The changes in ACT value were according to different factors. Pre CPB ACT value increased to 540±91 seconds when heparin was given to the patient before going on CPB, then CPB initiated, the ACT value increased to 697±46 seconds due to hemodilution factor. After aorta cross clamped patient was cooled down to 32±2˚C, we measured an increase in ACT value to 766±43 seconds. Before termination of CPB rewarming was started, temperature increased to 36±1˚C and the ACT value decreased to 538±49 seconds. In the end, after termination of bypass protamine was given and value of ACT was decreased to 113±14 seconds. So, this graph shows the increase and decrease in ACT values according to change in temperature and hemodilution (**Fig. 1**).

Ethical consideration

This study was ethically approved from the Department of Cardiac Surgery, Faisalabad Institute of Cardiology, Faisalabad, Pakistan.

Table 3: Analysis of effect of temperature and hemodilution on ACT values by Paired T-Test

					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	T	df	Sig.(2-tailed)
Pair 1	Baseline - pre-CPB	-395.38095	96.73907	21.11020	-439.41605	-351.34586	-18.729	20	.000
Pair 2	pre-CPB - Hemodilution	-156.90476	81.89194	17.87029	-194.18153	-119.62800	-8.780	20	.000
Pair 3	Hemodilution - Hypothermia	-69.66667	21.12187	4.60917	-79.28123	-60.05211	-15.115	20	.000
Pair 4	Hypothermia - Normothermia	228.14286	55.20171	12.04600	203.01534	253.27037	18.939	20	.000
Pair 5	Normothermia – Protamine	425.19048	43.95864	9.59256	405.18074	445.20021	44.325	20	.000

Table 4: Central Tendencies of ACT Values

Tests	Mean	N	Std. Deviation	Std. Error Mean
Baseline	145.0000	21	19.30285	4.21223
pre-CPB	540.3810	21	91.05354	19.86951
Hemodilution	697.2857	21	46.56946	10.16229
Hypothermia	766.9524	21	43.32722	9.45477
Normothermia	538.8095	21	49.58490	10.82031
Protamine	113.6190	21	13.74946	3.00038

Results

Before CPB was initiated, the averaged pre-CPB ACT was 541±90 seconds. After 5 minutes of initiation of CPB, Averaged ACT value increased as 697±46 seconds. This prolongation was due to prime volume present in CPB circuit. When CPB was initiated, it caused the dilution of clotting factors. As the P<0.005, it proves that methods in **Table 3** are significant.

The effect of hypothermia on ACT was apparent but less predictable. When the temperature reached at an average 32±2˚C, then the ACT value was averaged as 766±43 seconds. This decrease in temperature caused an increase in ACT value. As the P<0.005, it proves that methods in table 3 are significant.

Before termination of CPB, an average 36±1˚C temperature was achieved. The averaged ACT value (538±49 seconds) was decreased at rewarmed temperature. Which was proved significant as p<0.005. This large decrease is due to efficient working of enzymes at optimum temperature and other factors like urination.

The results of paired sample T-TEST were highly significant as the P value of each comparison is extremely small then zero.

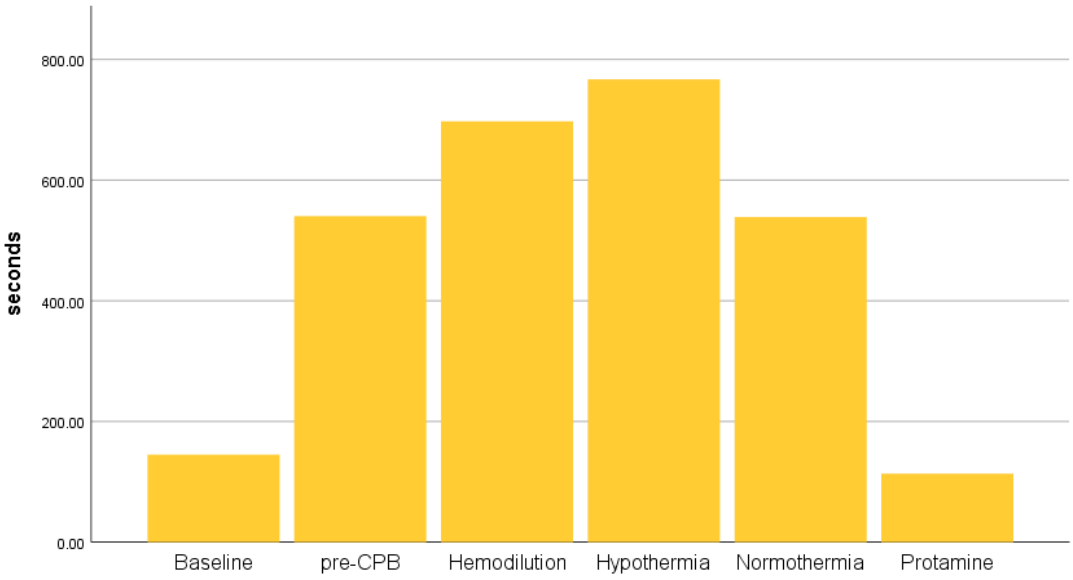

Fig. 1: Graphical interpretations of ACT values

Discussion

Activated clotting time is the most common method used worldwide to assess the clotting time of blood before and after CPB and in ICU. Its value depends on many factors but here we interpret only two of them. As we know from present studies that enzymes functioning e.g., clotting factors depends on temperature and other factors [3]. Bull *et al* explained the safe ranges for anticoagulation which starts from 300 seconds [6].

Before initiation of CPB heparin was used to raise the ACT value >480 seconds. When CPB started we study the change in this value due to hemodilution. It caused change in the averaged value of ACT from 540±91 seconds to 697±46 seconds, which explained the effect of prime volume present in the circuit. Perfusionist can control the change in ACT value if he reduces the volume of prime. Further that the dilution of clotting factors also causes prolongation of ACT (**Fig. 2**).

After the above prolongation, patient is cooled down to 32±2˚C which help to decrease the O2 requirements and metabolic rate. The decrease in temperature causes enzymes to lose their function and further prolongation of averaged ACT value from 697±46 seconds to 766±43 seconds. Decreased metabolism

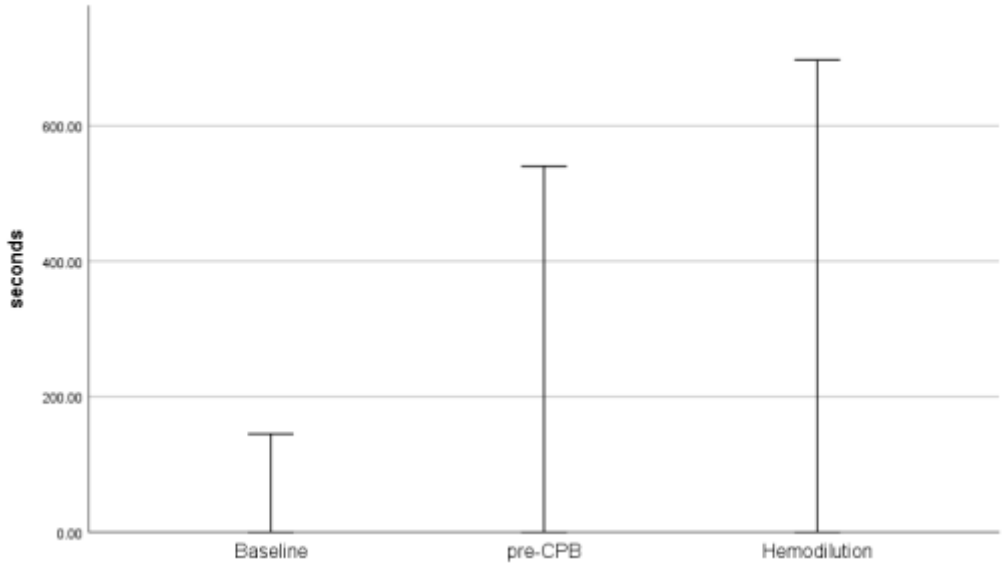

Fig. 2: Effect of hemodilution

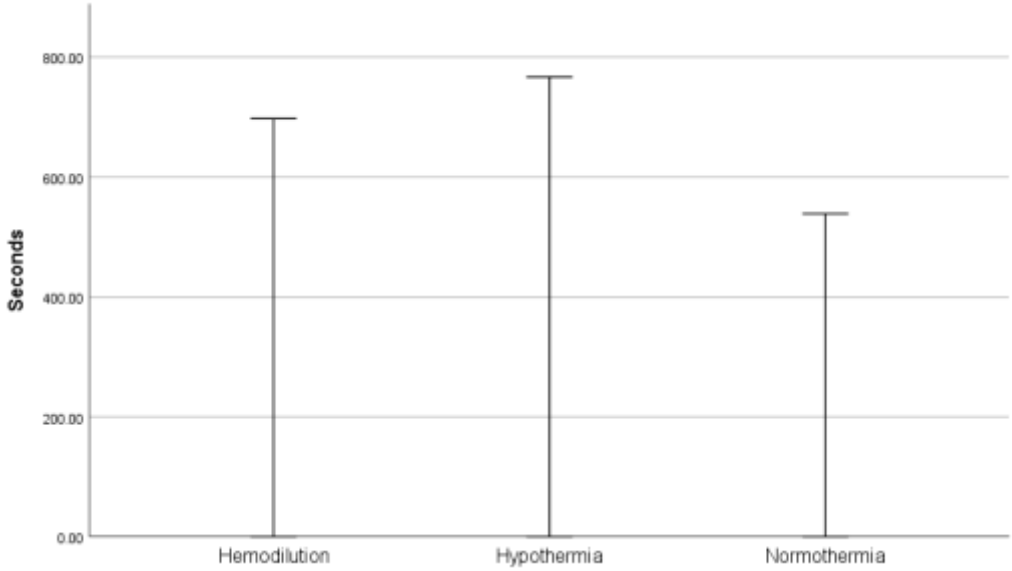

Fig. 3: Effect of temperature

and clotting factor activity cause an increase in anticoagulation. The P-value is less than 0.005, which proves that the results in table 3 are significant.

Before termination of CPB, rewarming was started and a change in ACT value was seen. The averaged ACT value change from 766±43 seconds to 538±49 seconds. This decrease is due to optimum temperature. As the temperature increased to normothermia, metabolic activity increased causing clotting enzyme to work efficiently at optimum temperature. As the time passed, the prime volume added at the start of CPB was also excreted as urine. So, it also contributes to decrease in ACT value (**Fig. 3**).

After termination, protamine was given, and ACT return back to baseline. In this study we observe the effect of temperature and hemodilution on activated clotting time. How these factors alter the value of ACT. It will help in better management of anticoagulation during and after CPB.

Conclusion

The activated clotting time value of blood has direct relationship with hemodilution because it causes increase in ACT of blood as blood volume increase as

shown in graph and inverse relationship with temperature, as we can see ACT value increase as the temperature decrease or vice versa. So, it will help to understand changes that occur in hemostasis during CPB. We can reduce heparin dose in trauma patients who are already at bleeding risk. The increase in coagulation during rewarming phase can be better managed by this knowledge. So, it will help in better management of anticoagulation during and after CPB.

Conflict of interest

The authors declare no conflict of interest.

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