

The use of Rotational Thromboelastometry (ROTEM) in Adult Cardiac Surgeries: Review Article

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ABSTRACT

Background: Severe hemorrhage is a common complication of cardiac surgeries, particularly those performed via cardiopulmonary bypass. Perioperative hemorrhage shows a spectrum of severity, with excessive bleeding being documented in 2% to 11% of patients. Cardiopulmonary bypass (CPB) is the primary cause of intraoperative hemorrhage.

Objective: improvement of outcome in cases undergoing elective cardiac surgery on cardio-pulmonary bypass by reducing blood products transfusion.

Material and methods: Rotational Thromboelastometry, long cardiopulmonary bypass term and Adult Cardiac Surgeries were searched for in PubMed, Google Scholar, and The Egyptian Knowledge Bank. Only the most current or comprehensive studies were included after the authors thoroughly filtered references from the pertinent literature, which comprised all the recognised studies and reviews. Documents written in languages other than English have been ignored due to a lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to qualify as scientific research.

Conclusion: Long cardiopulmonary bypass term, the greatest predictor of microvascular bleeding, is a distinct risk factor for development of death rate and illness following cardiac operation. Bleeding risk increases when the CPB duration exceeds 120 minutes. Clotting factor loss can also occur as a consequence of intraoperative cell-saving devices. Fibrinolysis is also induced by platelet dysfunction and clotting factor degradation, as plasminogen activation during CPB and heparinization both contribute to this process. Hypothermia may impair the function of platelets and enzymes. Platelet adhesion and aggregation are inhibited at body temperatures below 33 °C.

Keywords: ROTEM device, Cardiac surgery, HEPTTEM test.

INTRODUCTION

Cardiac surgeries are frequently associated with severe bleeding especially those carried out on cardiopulmonary bypass. Perioperative bleeding can range from minimal to substantial, with the latter occurring in approximately two percent to eleven percent of all cases ⁽¹⁾.

Abnormalities of the coagulation system in cardiac surgeries can be problematic, there are varieties of ways in which coagulation disturbances occur. Coagulopathy arises from platelet failure, hemodilution, depletion of coagulation factors, activation of fibrinolytic system, and presence of residual heparin and/or excessive protamine. Timely intervention is necessary to address excessive bleeding after surgery. This can be done by allogenic blood transfusion, the use of pharmacological hemostatic medications, or chest re-exploration if necessary. Any of these procedures were carried out to alleviate negative effects of bleeding is linked to more unfavorable clinical result. ACT is frequently assessed throughout and at end of CPB to detect appropriate dosage of heparin or protamine. ACT readings are influenced by factors such as heparin concentration, hemodilution, low platelet count, low fibrinogen, & excessive protamine ⁽²⁾.

A range of assays designed for monitoring hemostasis at the point of care have demonstrated utility across

diverse clinical contexts. Viscoelastic evaluation of clot formation, as ascertained through rotational thromboelastometry (ROTEM, TEM International, Munich, Germany) & thrombelastography (TEG, Haemonetics, Braintree, MA, USA), and impedance aggregometry, as determined by multiplate analyzer (Roche, Basel, Switzerland) & ROTEM platelet (TEM International), offer essentially two separate approaches to ascertain coagulation status ⁽³⁾.

The ROTEM instrument is equipped with four distinct analyzer channels, allowing for the concurrent and independent evaluation of all parameters. A wide range of ROTEM assays are accessible through the utilization of distinct activated reagents. Utilizing HEPTTEM test, it is possible to detect presence of coagulation inhibitors such as heparin and its impact on the process through comparison with INTEM ⁽⁴⁾. The aim of this work was improvement of outcome in cases undergoing elective cardiac surgery on cardio-pulmonary bypass by reducing blood products transfusion.

Bleeding in cardiac surgery:

It is common for patients undergoing cardiac surgery to experience peri-operative hemorrhage. Serious & potentially fatal hemorrhaging may be undetectable and not necessitate medical attention. Reportedly, 2-11% of cases experience excessive hemorrhage ⁽¹⁾. With a 2.6

percent overall incidence, blood loss is defined as 1.5 ml/kg/hour lost over 6-hour period or early reoperation. Prior research on postoperative bleeding that utilized packed red blood cells (PRBC) transfusion as a surrogate for bleeding evaluation discovered that ten to fifteen percent of cases received a minimum of four PRBC units within the initial twenty-four hours. Adverse hemorrhage following cardiac surgery can be attributed to a variety of factors, which can be further categorized into medical & surgical causes ⁽⁵⁾. However, because transfusion strategies vary considerably among centers, the PRBC transfusion rate may not provide accurate estimation of hemorrhage. Blood loss from chest drains has been utilized in few recent researches to evaluate hemorrhage more directly; however, these researches employed a predetermined and protracted observation period and did not account for body weight adjustments ⁽⁶⁾.

In 2014, a comprehensive detection of hemorrhage during surgical procedures in mature cases undergoing cardiac operation was introduced. The UDPB is derived from 9 events that take place either during surgery or within the initial 24 hours after the operation: 1: Delayed closure of the sternum, 2: Amount of fluid drained from the chest after surgery, 3: Transfusion of packed red blood cells 4: FFP transfusion, 5: Platelet transfusion, 6: Cryoprecipitate transfusion, 7: Utilization of factor concentrates, 8: Utilization of recombinant activated factor VII, and 9: Surgical re-exploration. The primary cause of excessive post-operative bleeding in most cases is surgical in nature & typically occurs at anastomotic sites (suture lines), side branches of arterial or venous conduits, substernal soft tissues, sternal suture sites, bone marrow, periosteum, raw surfaces resulting from previous surgery, or pericarditis. Previous investigations have shown that the surgical reasons for bleeding that require further study might vary from thirty-five percent to one hundred percent ⁽⁷⁾.

Bleeding due to medical causes is noted after complex or redo surgeries & is frequently related with coagulopathies.

Risk factors for medical bleeding can be classified to: pre-operative factors:

During CABG surgery, when double antiplatelet therapy is administered and in cardiac surgeries involving CPB, being male is a prognostic factor for experiencing substantial blood loss. Thromboelastography measurements indicate that healthy women have more procoagulant profile than healthy males. This is attributed to their quicker fibrin production rate, stronger clot strength, & superior viscoelastic characteristics ⁽⁸⁾.

The excessive usage of antiplatelet medicines in individuals with acute coronary syndromes is a significant issue due to the presence of qualitative platelet abnormalities. Preoperative platelet dysfunction can

occur due to the use of antiplatelet medicines. Having low platelet count of less than $100 \times 10^6/L$ before surgery is significant risk factor for hemorrhage & the need for large amounts of transfusions of blood after the operation. Heparin-induced thrombocytopenia (HIT) is another possible cause of thrombocytopenia that you should be aware of. Around eight percent of people who receive heparin acquire the antibodies linked with HIT, & between one and five percent of individuals who are treated with heparin go on to develop HIT. Cases who have hepatic dysfunction, residual warfarin impact, deficits in vit K-dependent clotting factors, von Willebrand's disease, or are undergoing thrombolytic treatment are at a higher risk of experiencing severe bleeding following CPB ⁽⁹⁾.

Intraoperative factors

CPB is the primary cause of bleeding during surgery. Extended duration of CPB is distinct risk factor for increased mortality & morbidity following cardiac operations, & it is the most accurate indicator of microvascular hemorrhage. There is a higher likelihood of experiencing bleeding if the length of CPB exceeds 120 minutes ⁽¹⁰⁾.

The utilization of intraoperative cell preservation devices also leads to a depletion of clotting factors. Clotting factor degradation & platelet dysfunction also led to fibrinolysis, which occurs as a result of plasminogen activation through CBP. Additionally, heparinization itself creates condition of increased fibrinolysis. Hypothermia can impair platelet & enzyme activity. Platelet aggregation and adhesion diminish at temperatures below 33°C ⁽¹¹⁾.

Postoperative factors

Heparin rebound is well recognized as the primary factor leading to bleeding during the post-bypass phase. The phenomenon can be best described as the return of reduced blood clotting capacity after sufficient neutralization of heparin has been achieved ⁽¹²⁾.

Rotational thromboelastometry (ROTEM ®)

The whole blood viscoelastic hemostasis analyzer known as rotational thromboelastometry (ROTEM ®, TEM International GmbH, Munich, Germany & TEM Systems, Inc., Durham, NC, USA) has its origins in the original thrombo-elastography system, which Helmut Hartert introduced in 1948. In 1990s, Andreas Calatzis upgraded ROTEG to ROTEM system ⁽¹³⁾.

ROTEM ® Device Components:

The current iteration of ROTEM ® system, known as the ROTEM ® delta, includes small measurement unit with 4 temperature-adjusted independent measurement channels, prewarming plate, reagent tray, & integrated personal computer. This configuration permits connection

& remote access to LIS. A touchscreen that is connected to the device and supported by software is utilized to control device & specialized ROTEM® software. This feature enhances device's usability & minimizes the differences in test results caused by different operators⁽¹⁴⁾

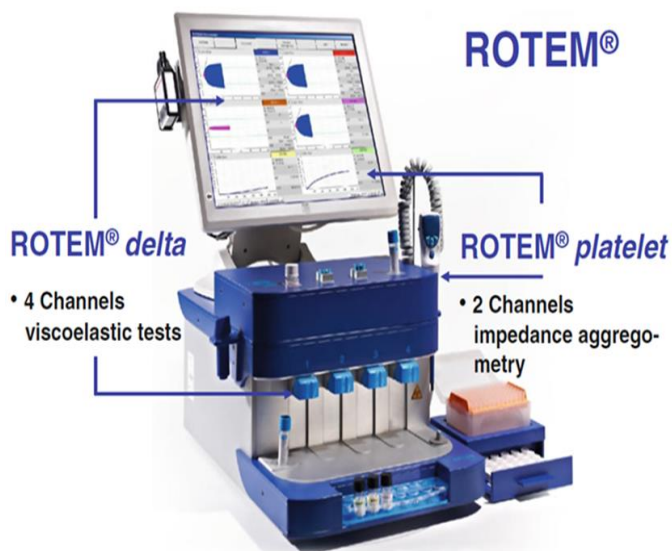


Figure (1): ROTEM® delta device, which utilizes thromboelastometry, combined with the ROTEM® platelet module, which use whole blood impedance aggregometry. Provided by Klaus Görlinger, Tem International⁽¹⁵⁾

Measurement Technique:

ROTEM® gadget has four separate viscoelastic measurement channels, which enable the use of a range of particular tests⁽¹⁶⁾. The ROTEM® gadget is capable of promptly detecting & distinguishing among various coagulopathies, as hypofibrinogenemia & thrombocytopenia. Its purpose is to help in defining appropriate hemostatic treatment for cases experiencing bleeding. Every measuring channel consists of disposable cuvette that is held in temperature-controlled metal cup-holder. Additionally, there is disposable pin attached to movable axis, which is supported by ball-bearing. ROTEM® axis undergoes oscillation in a reciprocating manner, spinning at an angle of 4.75° in both directions, completing twelve cycles every minute.

ROTEM® Assays:

Thromboelastometric tests employ citrated whole blood, with a volume of 300 µL each assay. This blood is then recalcified and stimulated using tissue factor (extrinsic pathway), ellagic acid (intrinsic pathway), or ecarin (direct prothrombin activation). Certain tests may include additional additives. The ROTEM® system offers a range of activated assays that significantly enhance diagnostic accuracy of device contrasted to a single-assay system⁽¹⁷⁾. Available tests include extrinsically activated assays (EXTEM, FIBTEM, and

APTEM), intrinsically activated assays (INTEM & HEPTEM), ecarin-activated assay (ECATEM), & non-activated assay (NATEM). ECATEM is exclusively accessible in Europe. Similar to PT, EXTEM tests are triggered by the addition of calcium chloride (in the startem® reagent, with concentration of 0.2 mol/L) & tissue thromboplastin (in the rextem® reagents, which consist of recombinant tissue factor & phospholipids). Therefore, while coagulation is triggered by extrinsic route, the early production of thrombin & subsequent clotting mostly relies on functioning of coagulation factors VII, X, V, II, & fibrinogen in EXTEM test. Hence, utilization of both EXTEM and FIBTEM enables differentiation among thrombocytopenia & hypofibrinogenemia. By comparing clot strength of EXTEM & FIBTEM. It is possible to estimate contribution of platelets to hardness of clot, which is often referred to as PLTEM by some writers⁽¹⁸⁾.

The APTEM test is a third assay that is triggered externally & involves usage of antifibrinolytic medication, previously aprotinin & currently tranexamic acid (taptem®). This test allows for evaluation of anti-fibrinolytic therapy in a laboratory setting. The ECATEM test employs viper venom ecarin as a stimulant. Ecarin immediately transforms prothrombin into meizothrombin, a form of thrombin with inherently low activity. Importantly, meizothrombin is suppressed by hirudin & other direct thrombin inhibitors (as hirudin, argatroban, bivalirudin, & dabigatran), but not by heparin⁽¹⁹⁾.

ROTEM® Parameters:

ROTEM® reference ranges may exhibit modest variations across different countries (such as Europe and the USA) and even between different hospitals. Thus, these reference ranges serve as a general guide and it is advisable to construct reference ranges customized to each institution. The results may be influenced by several factors as reference population, age, blood collecting containers & procedure, sample transit, & other pre-analytic parameters. It is worth mentioning that there have been published reference ranges for babies and children based on their age, as well as reference ranges for pregnant women based on the trimester of their pregnancy⁽²⁰⁾.

Parameters for the activation of coagulation & polymerization of blood clots:

Thromboelastometric CT is the duration, measured in seconds, from the beginning of test until clot firmness amplitude of two mm is achieved. In tissue factor activated testing, CT is typically obtained in around 1 minute. CT is measure of how quickly thrombin is produced. It is primarily influenced by enzymatic activity of coagulation factors (either extrinsic or intrinsic, based on specific test), levels of anticoagulants & fibrin split products, & the presence of tissue factor on circulating cells (as monocytes or malignant cells)⁽²¹⁾.

Clot firmness parameters:

MCF in mm is crucial metric in ROTEM®. It represents the highest amplitude of clot firmness achieved throughout test. Clot amplitude is an indicator of clot's mechanical strength & is primarily determined via factors such as Plts' count & function, fibrin concentration & polymerization, factor XIII activity, & colloids. The EXTEM & INTEM A10 and A5 parameters are positively associated with Plts' count & fibrinogen concentration. Similarly, the FIBTEM A10 & A5 parameters are strongly correlated with plasma fibrinogen concentration. Additionally, the PLTEM A10 & A5 parameters, as well as EXTEM A10 & FIBTEM A10 parameters, show significant correlation with platelet count ⁽²²⁾.

Clot lysis parameters:

Clot lysis metrics maximal lysis & lysis indices 30 & 60 offer insights into functioning of fibrinolytic enzymes, fibrinolytic inhibitors, & factor XIII. ML discovered throughout the run is defined as percentage variance among MCF & the lowest amplitude seen following MCF. LI30 & LI60 represent the proportion of MCF that remains after thirty minutes and sixty minutes following CT, respectively. On the other hand, TEG ® lysis parameter LY30 & LY60 measure degree of lysis as a percentage of MA, 30 & 60 minutes after achieving MA. ROTEM ® lysis onset time is duration, measured in seconds, from the initiation of CT until fifteen percent of CL is attained ⁽²³⁾.

ROTEM ® limitations:

One significant drawback of conventional viscoelastic testing is its lack of sensitivity to impact antiplatelet medications as cyclooxygenase-1 inhibitors & ADP (P2Y₁₂)-receptor inhibitors. The restriction arises from the excessive production of thrombin in viscoelastic test systems, that obscures impact of antiplatelet medications via activating platelets through thrombin-receptor pathway (specifically, protease-activated receptor 1 & 4) ⁽²⁴⁾.

ROTEM ® platelet module:

The ROTEM® delta may be integrated with ROTEM® platelet module, that has been granted the CE mark in Europe since November 2013. ROTEM® delta provides four viscoelastic channels, as well as 2 additional channels for whole blood impedance aggregometry. Arachidonic acid (ARATEM), adenosine di-phosphate (ADPTEM), & thrombin receptor-activating peptide-6 (TRAPTEM) are appropriate substances for activating ROTEM ® platelet. The associated reagents are prepared as lyophilized single-use reagents that are user-friendly and convenient to use. Whole blood impedance aggregometry has shown efficacy in detecting effects of COX-1 inhibitors & ADP-receptor inhibitors. Additionally, it has the ability to forecast stent thrombosis, ischemic events, hemorrhage, platelet

transfusion, & mortality in fields of interventional cardiology, cardiac surgery, severe trauma, & sepsis. Furthermore, whole blood impedance aggregometry can be utilized to monitor effects of medications, as desmopressin & tranexamic acid, on platelet function ⁽²⁵⁾.

Aggregometry:

Platelets have crucial role in process of blood clotting, known as haemostasis. When blood artery is injured, platelets have the ability to stick to the damaged vessel wall & initiate a process that results in the accumulation of more platelets. This, together with other components of blood, leads to creation of firm blood clot ⁽²⁶⁾.

ROTEM® platelet module is impedance aggregometer designed to evaluate Plts' function in anticoagulated whole blood samples. The method measures both the quantity and quality of platelet aggregation by analysing the changes in electrical impedance that occur following platelet activation using various substances ⁽¹⁴⁾.

The ROTEM® platelet module is designed for use in patients receiving antiplatelet pharmaceuticals or other medications that may affect platelet function. It is also intended for use in cases suspected of having Plts dysfunction owing to extracorporeal circulation, trauma, sepsis, or other causes. This product is intended for usage in clinical labs, hospitals, or other clinical care facilities by healthcare professionals. ROTEM® platelet module is utilised in connection with ROTEM® delta system, however it is not mandatory to be supplemented via viscoelastic testing ⁽¹⁴⁾.

ROTEM® platelet system: Two channels that allow for the simultaneous performance of experiments. It can be utilised during the execution of thromboelastometry measurements and in conjunction with ROTEM® delta. Electronic pipetting enables usage of pipettes outside of established laboratories. Prepared for immediate usage, these reagents are designed for one-time usage ⁽²⁷⁾.

Detection technique: impedance aggregometry with ROTEM® platelet:

The process involves transferring whole blood into cuvette that contains stirring bar & specialised electrodes, which are then activated with certain voltage. Prior to initiating plt aggregation, impedance baseline is established. Upon the addition of aggregating agents, Plts become activated & proceed to aggregate on wire surface of test cuvettes, resulting in an increase in impedance among the wires. Magnetic stirrer is used to prevent the settling of blood cells through 3-minute incubation period. The temporal evolution of electrical impedance is quantified. Extent of Plts engaged in covering electrodes via aggregation is directly proportional to it. The measurement findings are analysed using dedicated software. ⁽¹⁴⁾.

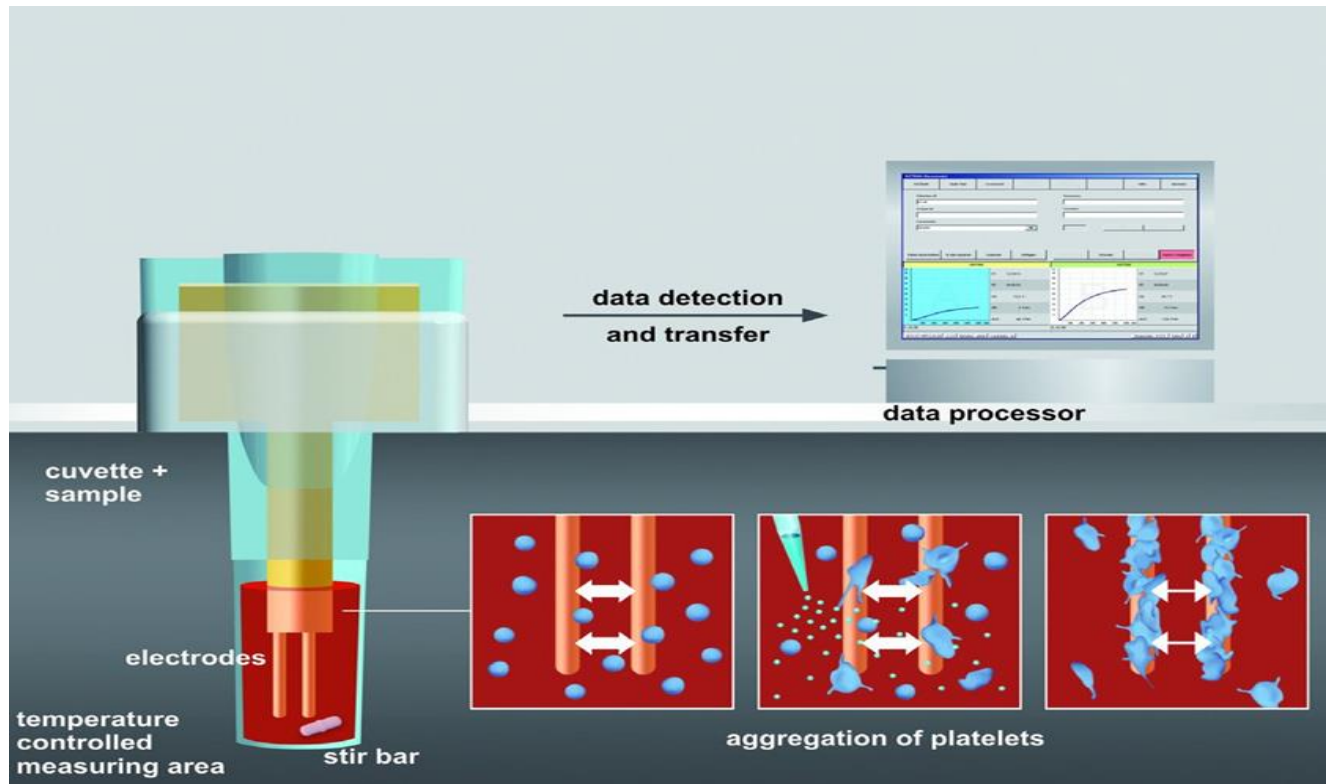


Figure (2): ROTEM® platelet detection method.

parameters of ROTEM® platelet analysis⁽¹⁴⁾

AUC (Area under the curve):

AUC denotes cumulative area under the aggregation curve during initial measurement period of up to six minutes of runtime. AUC provides a comprehensive measure of platelet aggregation.

- **MS (Maximum Slope):**
Maximum slope refers to the MS of the aggregation graph. MS represents the aggregation rate.
- **A6 (Amplitude at 6 minutes):**
A6 indicates impedance reading six minutes after test commenced. The parameter A6 quantifies the degree of platelet aggregation.

ROTEM® platelet tests:

By incorporating several supplementary tests and parameters, the ROTEM® platelet analysis enhances diagnostic capability via differentiating the effects of various platelet drugs on platelet aggregation. Permit platelet dysfunction caused by extracorporeal assist devices or surgery, for instance, to be detected. Plts are stimulated with arachidonic acid in **ARATEM**. An illustration of this is the assessment of Plt function in

cases undergoing cyclooxygenase inhibitor treatment (as, acetylsalicylic acid). Plts are stimulated with adenosine diphosphate in **ADPTEM**.

An evaluation of platelet function is conducted on patients who are undergoing treatment with ADP receptor antagonists, such as clopidogrel. Platelets are stimulated with thrombin receptor activating peptide in **TRAPTEM**. Plt function is evaluated in cases undergoing treatment with GP IIb/IIIa receptor antagonists (abciximab) or PAR-1 receptor antagonists (as, vorapaxar)⁽¹⁴⁾.

ROTEM® platelet expected values:

The presented data are typical ROTEM® aggregometry values, which are obtained through the analysis of healthy cases without aggregation disorders who do not require antiplatelet medications. These values are susceptible to variation contingent upon the population under examination. To establish respective 'local' reference ranges, it is therefore advised that, prior to implementing ROTEM® platelet, a subset of patients devoid of pathological findings be analysed. The reference values utilised for the various assays vary according to the type of sample utilised (tubes containing citrate, heparin, or hirudin) (Table D)⁽²⁸⁾.

Table (A): Platelet preliminary reference ranges for **ROTEM®** ⁽¹⁴⁾ regarding citrated specimens

Test / Parameter	AUC	A6	MS (Ohm/min)
ADPTEM (n=20)	56-139	16-38	4-11
TRAPTEM (n=175)	61-156	15-36	5-14
ARATEM (n=20)	70-153	19-41	6-13

regarding heparinized samples

Test / Parameter	AUC	A6	MS (Ohm/min)
ADPTEM (n=20)	57-133	16-34	4-12
TRAPTEM (n=60)	66-169	15-38	6-18
ARATEM (n=20)	69-144	17-37	6-14

regarding hirudinized samples

Test / Parameter	AUC	A6	MS (Ohm/min)
ADPTEM (n=20)	86-201	23-52	7-17
TRAPTEM (n=60)	67-155	17-37	6-15
ARATEM (n=20)	84-193	21-52	7-16

Evaluation of the ROTEM® platelet examination:

Platelet dysfunction, whether induced by drugs or not, can be identified through the utilization of decreased AUC, A6, and MS test outcomes ⁽¹⁴⁾ Cyclooxygenase inhibitors (as, acetylsalicylic acid) may impede Plt aggregation in patients undergoing treatment. Ascertained through the ARATEM test, ADP receptor antagonists (as, clopidogrel) may impede Plt aggregation in patients undergoing treatment.

The aforementioned will be identified through the ADPTEM test. When dual antiplatelet therapy (e.g., clopidogrel and acetylsalicylic acid) is administered to patients, Plt aggregation may be impaired. detection of this will be achieved using ADPTEM & ARATEM. Cases undergoing treatment with PAR-1 receptor antagonists (as, vorapaxar) may experience an impairment in platelet aggregation. TRAPTEM will detect this phenomenon.

Platelet aggregation may be impaired in patients whom GP IIb/IIIa inhibitors (as, abciximab) are administered. All of the following assays will detect this: ADPTEM, TRAPTEM, & ARATEM.

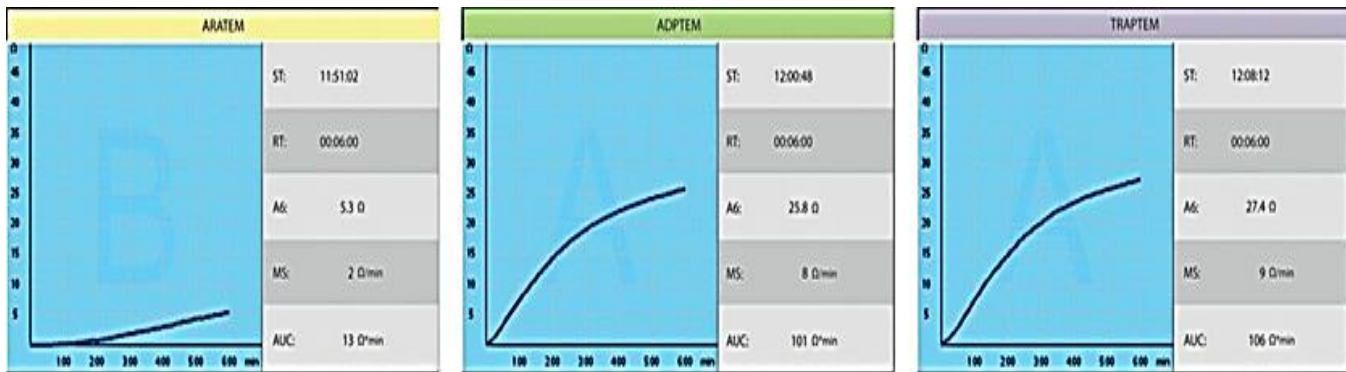
Plt aggregation may be impaired in the case of non-drug-induced platelet dysfunction, such as thrombocytopenia, extracorporeal assist devices, trauma, surgery, infection, or sepsis. This is detectable by all three assays (ADPTEM, TRAPTEM, & ARATEM). Nevertheless, the impact might be more conspicuous on the TRAPTEM test in cases of trauma and sepsis, respectively. ⁽²⁸⁾.

Limitations:

Abnormal aggregation may be observed in individuals with low platelet count.

Assessment of the ROTEM® platelet analysis ⁽¹⁴⁾

A: case treated with acetylsalicylic acid:



B: case treated with voropaxar:

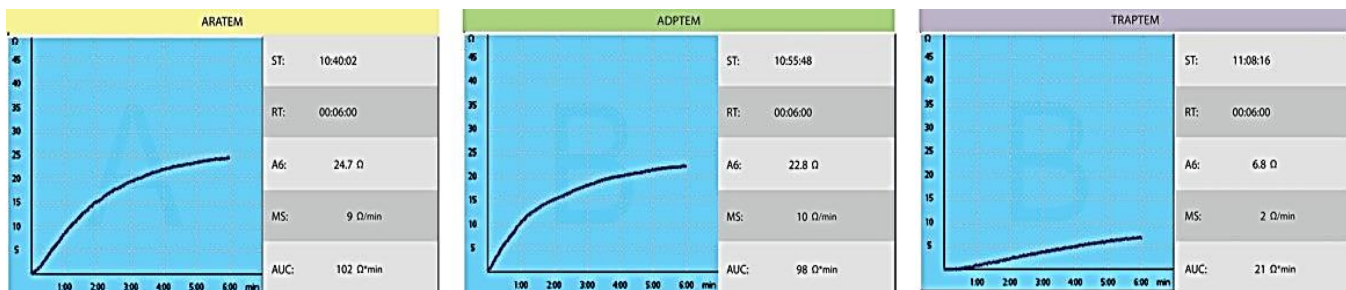


Figure (3): Instances of diminished platelet aggregation following medication use.

Ethical Considerations: The research project received ethical approval from the Department of Anesthesia & ICU at Suez Canal University, Egypt, as well as the Research Ethics Committee of the Faculty of Medicine, Suez Canal University.

DECLARATIONS

- **Consent for publication:** All author has granted permission for the work to be submitted.
- **Funding:** No fund
- **Availability of data & material:** Available
- **Conflicts of interest:** No conflicts of interest.
- **Competing interests:** None.

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