Medicinski podmladak

Medical Youth

Mini review article

CLINICAL UTILITY OF ROTATIONAL THROMBOELASTOMETRY IN DETECTING HEMOSTATIC DISORDERS

KLINIČKI ZNAČAJ PRIMENE ROTACIONE TROMBOELASTOMETRIJE U DETEKCIJI POREMEĆAJA HEMOSTAZE

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Abstract

Hemostasis represents an equilibrium between procoagulant and anticoagulant processes, but once this balance is shifted to one side, it leads to coagulopathy presented by pathological bleeding or thrombosis. Many conditions could cause coagulopathy. The most common are sepsis, severe traumas and malignancies. Widely used conventional coagulation tests (CCTs), focused only on clot initiation, are primary used to detect hypocoagulability. Viscoelastographic tests (VET), like rotational thromboelastometry (ROTEM), can detect problems in different stages of coagulation, from initiation thought clot elongation and propagation, to the clot lysis and might reveal both, hypercoagulability and hypocoagulability. Rotational thromboelastometry have gained popularity in the care of patients with TIC, as a tool to guide transfusion support. Nowadays it is widely used in other medical specialties, as well. Several studies in septic patients pointed out hypocoagulable ROTEM pattern as a predictor of poor prognosis. Additionally, there is great interest of ROTEM usage in malignancies, although limited research is currently available. It suggests ROTEM have the ability to identify a patient in high risk of thrombosis. Further investigation trough randomized studies is needed to confirm ROTEM utility and to help in making a consensus about its use in different medical occasions.

Keywords:
coagulopathy,
rotational thromboelastometry,
sepsis,
trauma induced coagulopathy,
malignancies

The authors declare no conflicts of interest.

doi:10.5937/mp71-27853
Editorial board: podmladak.med.bg@gmail.com
e-ISSN: 2466-5525

Sažetak

Hemostaza predstavlja ravnotežu između prokoagulantnih i antikoagulantnih procesa i, jednom narušena, vodi do koagulopatije u vidu krvarenja ili tromboze. Mnoga stanja mogu da uzrokuju koagulopatiju, ali su najčešća sepsa, trauma i maligniteti. Široko primenjivani konvencionalni koagulacioni testovi (KKT) primarno se koriste za detekciju hipokoagulabilnosti i fokusiraju se samo na inicijaciju procesa koagulacije. Viskoelastografski testovi (VET), kao što je rotaciona tromboelastometrija (ROTEM), testovi su iz pune krvi kojima mogu da se detektuju poremećaji u različitim fazama koagulacije, počevši od inicijacije, preko elongacije i propagacije, pa sve do lize ugruška, te mogu da ukažu i na hipo- i na hiperkoagulabilnost. Rotaciona tromboelastometrija se široko primenjuje kod pacijenata sa traumom i u velikim hirurškim intervencijama kao sredstvo na osnovu čijih rezultata se određuje potreba za primenom transfuzijskih mera. Nekoliko studija, sprovedenih na pacijentima sa sepsom, pokazalo je da je hipokoagulabilan ROTEM obrazac prediktor loše prognoze. S druge strane, danas postoji veliki interes za primenu ROTEM-a u malignitetima. Rezultati dosadašnjih studija ukazali su da je na osnovu ROTEM-a moguće identifikovati pacijenta u povećanom riziku za razvoj tromboembolijskih komplikacija. Biće neophodna dodatna istraživanja i randomizovane studije da bi se potvrdili značaj i uloga ROTEM-a i pomoglo u donošenju konsenzusa o njegovoj primeni u različitim oblastima medicine.

Ključne reči:
koagulopatija,
rotaciona tromboelastometrija,
sepsa,
trauma,
maligniteti

Introduction

Hemostasis is a dynamic process, and when triggered, it starts a cascade of actions resulting in clot formation localized only in area of injured blood vessel with the aim to prevent excessive blood loss and to help tissue repair (1). Traditionally, its consists of three consecutive steps: primary hemostasis, starting upon vessel injury and resulting in platelet plug formation; secondary hemostasis, with forming fibrin polymers via activated clotting factors leading to clot propagation, and its termination; and fibrinolysis, where plasminogen has a main role in fibrin cleavage to fibrin degradation products (FDP) and establishment of a normal bloodstream. Normally, hemostasis represents an equilibrium between procoagulant and anticoagulant processes, but once this balance is shifted to one side, it leads to coagulopathy presented by pathological bleeding or thrombosis (1). Many conditions could cause hemostatic disorders: sepsis, shock, massive burns, major surgeries, cardiac arrest, massive mechanical traumas and malignancies. Disseminated intravascular coagulopathy (DIC) plays a central role in traumas and sepsis, in whom diffuse fibrin deposition and consumption of all clotting factors and platelets leads to greater hemorrhage risk. Malignancy associated coagulopathy (MAC) and its mechanism are not fully understood yet, but procoagulants, adhesion particles and soluble mediators produced by tumor cells seem to play major role (2). Comparing DIC, happening in only few hours when triggered, in MAC, a shift to procoagulants happens over a much longer time, leading to a risk of thromboembolic complications (2).

Widely used conventional coagulation tests (CCTs) failed to assess all this coagulation problems, so there is a need for other tests. Viscoelastographic tests (VET), like thromboelastography (TEG) and rotational thromboelastometry (ROTEM), can detect problems in different stages of coagulation, from initiation through elongation to the clot lysis, and might reveal both hypercoagulable and hypocoagulable state.

Rotational thromboelastometry

Rotational thromboelastometry (ROTEM) is VET, whereby a citrated whole blood is placed in a cuvette into which a rotating pin is immersed. As a clot forms, a viscoelasticity induces increasement of torque between cuvette and pin, and later on with fibrinolysis this torque decreases. This changes in torque are registered by a transducer providing a special graphic record (**figure 1**) (3, 4).

Commonly used ROTEM parameters are the following: clotting time (CT, period to 2 mm amplitude of the clot), clot formation time (CFT, time to accomplish amplitude from 2 mm to 20 mm), α-angle (angle of tangent at 2 mm amplitude), amplitude 5, 10, 20 (A5, A10, A20, clot firmness in 5th, 10th or 20th minute), maximum clot firmness (MCF, overall clot strength), lysis at 30 minutes (LI30, percent decrease in amplitude 30 minutes after achieving MCF), maximum lysis (ML, overall lysis at the end of the test) (5). Normal ranges for all variables are shown in Table 1 (**table 1**).

Depending on the substrate added into cuvette, in addition to phospholipids and calcium, several ROTEM tests are started. The EXTEM is started by adding a tissue factor and it imitates extrinsic pathway; the INTEM is run by ellagic acid and imitates intrinsic pathway of coagulation; the FIBTEM is initiated like EXTEM but by adding of cytochalasin D, platelet cytoskeleton is inhibited, so the whole clot formation depends on fibrinogen. Comparing results of EXTEM and FIBTEM, thrombocytopenia could be distinguished from hypofibrinogenemia or poor fibrinogen function. The APTEM is run like EXTEM, but after an antifibrinolytic agent is added, results may reveal

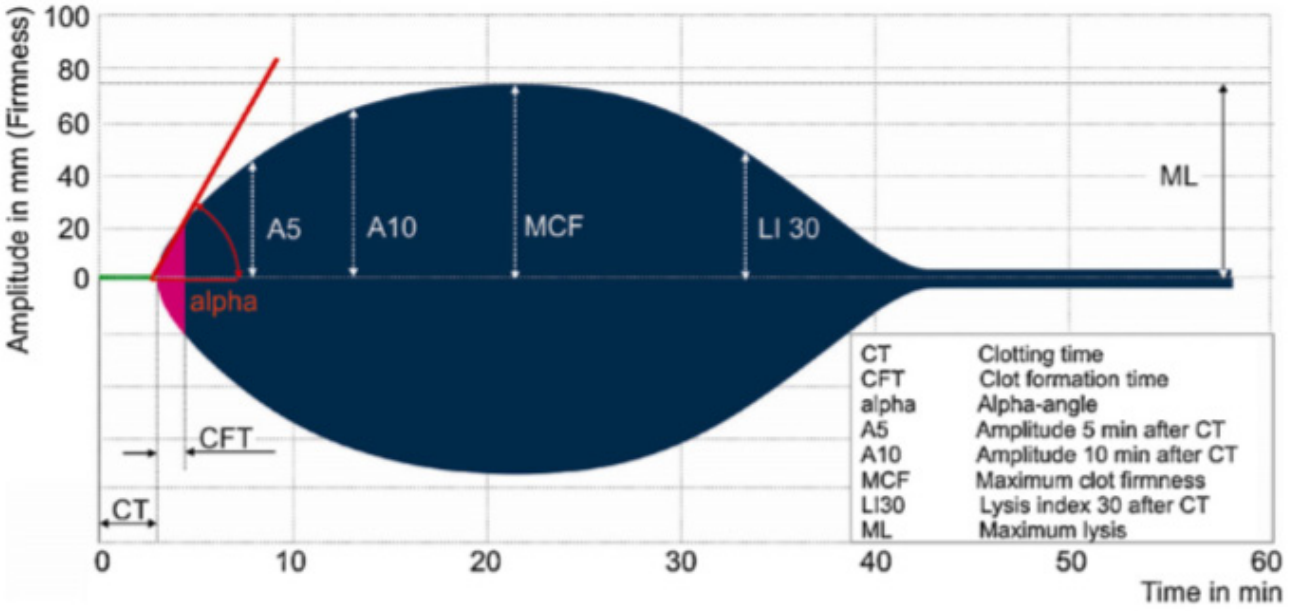

Figure 1. Illustration of ROTEM graphic record showing all faze of hemostasis: initiation (CT), propagation and elongation (α, A5, A10, MCF) and lysis (LI30, ML) – Tanaka et al. (4)

Table 1. ROTEM parameters, normal ranges

	CT (s)	CFT (s)	Alpha (°)	A10 (mm)	A20 (mm)	MCF (mm)	ML (%)
EXTEM	38 - 79	34 - 159	63 - 83	43 - 65	50 - 71	50 - 72	0 - 15
INTEM	100 - 240	30 - 110	70 - 83	44 - 66	50 - 71	50 - 72	0 - 15
FIBTEM	38 - 62	/	/	7 - 23	8 - 24	9 - 25	/

hyperfibrinolysis as a main coagulation problem. Lastly, the HEPTEM contains heparinase, in addition to INTEM reagents, and is used to diagnose systemic heparin activity in comparation to INTEM (4).

Rotational thromboelastometry evaluates entire process of coagulation, from initiation, propagation and elongation, to fibrinolysis at the end. In contrast to CCTs, ROTEM provides a full information of cumulative effects of platelets, clotting factor, white and red blood cells, fibrinogen and whole fibrinolytic system, and most closely imitates hemostatic process in vivo. According to all above mentioned, ROTEM could asses both hypo or hypercoagulability (2). Authors suggest that, with normal hemostasis, ROTEM graphic record is shovel shaped (**figure 2**), with an ideal handle length (CT), blade slope (α-angle), blade width (MCF), and blade tip (LI30). Continuing the analogy, the shovel shape in hypocoagulability has a long handle (prolonged CT) with a narrow and pointed blade (decreased MCF, increased LI30). On the other end of the spectrum, the shovel shape in a hypercoagulable state has a short handle and a wide blade with an absent tip, presented by shortened CT / CFT, increased MCF and decreased LI30 (2).

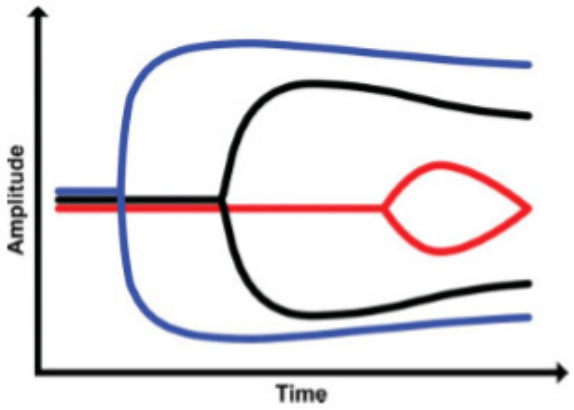

Figure 2. Simplified ROTEM graphic record. Black shovel represents a normal hemostasis, while red and blue represent hypocoagulability and hypercoagulability, respectively – Walsh et al. (2)

ROTEM and trauma induced coagulopathy

Trauma is a serious global health problem and one of the leading causes of death mainly in young individuals. Trauma induced coagulopathy (TIC) still remains a major challenge, and with hypothermia and acidosis presents a "lethal triad" (6). Causes of TIC are multifactorial, including consumption and dilution of coagulation factors and platelets, dysfunction of platelets and the coagulation system, increased fibrinolysis, dilution of the coagulation components by the infusion of colloid, hypocalcemia and DIC (6, 7). Coagulation monitoring is essential to directed care, and there are two main obstacles with CCTs: they do not reveal a coagulopathy far enough and their results cannot be obtained fast enough. Previous studies have showed decreased fibrinogen level and platelets count, prolonged APTT and PT in TIC, and furthermore TIC is usually diagnosed when INR (International Normalized Ratio) is > 1.2 or even > 1.5 (7-9). Several studies have dealt with the use of ROTEM in TIC and all have showed signs of hypocoagulability with prolonged CT and CFT, significantly shortened A5, A10 and MCF (7, 10, 11). According to this observation, even clot firmness 5 minutes after test has started could alert clinician to a possibility of coagulopathy. Knowing that fibrinolysis is one of a central mechanism of TIC, Raza et al. aimed to identify a ROTEM ability to reveal it. However, comparison of ROTEM with other fibrinolysis assays (plasmin–antiplasmin (PAP) complex and D-dimer) showed that ROTEM is less sensitive in distinguish normal and pathological fibrinolysis (12).

Current transfusion strategies in TIC focus on replenishing circulatory volume by transfusing blood component therapy in fixed ratios that mimic whole blood concentration, resulting in high plasma and platelets transfusion. According to CCTs, when there is microvascular bleeding and: a PT or APTT > 1.5 times normal fresh frozen plasma (FFP) is mandatory, platelet count < 50 x 10^9/L, platelet transfusion is needed, or fibrinogen concentration <1 g/L there is a need for cryoprecipitate. Red blood cell (RBC) transfusion is used when hematocrit is 21-24 %, or hemoglobin level < 80 g/L (6). However, evidences have showed increased morbidity and mortality in trauma patients received massive transfusions (13). Massive RBC transfusion deteriorate coagulopathy due to dilution of coagulation factors and platelets, as well as due to pH decrease, while by massive transfusion of FFP considerable amount of citrate in it leads to hypocalcemia (6). As a result, efforts now focus on methods to reduce blood component therapy, and that is where ROTEM takes its place (13).

Several studies pointed out ROTEM parameters could identify patients in need for massive transfusion. In the study of Davenport et al., A5 ≤ 35 mm was predictive for both RBC and FPP massive transfusion, with the ability to identify coagulopathic patients more than PT, suggesting a normal ROTEM trace may allow timely termination of massive hemorrhage protocols (10). Authors have suggested cut off values of ROTEM parameters and hemostatic interventions required based on them in trauma patients and in major surgeries. In the study of Schochl et al, threshold of FIBTEM MCF < 10 mm was used to guide transfusion of fibrinogen concentrate (FC) and EXTEM CT > 1.5 times normal used to guide PCC (prothrombin complex concentrate) administration. The authors were able to demonstrate a reduction in the number of RBC units transfused (14). One of the proposed algorithms for transfusion guide according to ROTEM, suggests: cryoprecipitate, FFP of FP if FIBTEM MCF is 8-10 mm or FIBTEM A10 < 5mm, platelet transfusion if EXTEM MCF < 45mm, EXTEM MCF < 35 mm, ML > 15 % and resolution of clot breakdown in APTEM are indicative for systemic hyperfibrinolysis and use of tranexamic acid should be considered (4). Considering all above mentioned, VETs are currently recommended as a routine tool for coagulation monitoring in trauma patients (9).

ROTEM in sepsis - from hypercoagulability to hypocoagulability

Sepsis is frequently associated with hemostatic disorders. Spectrum of coagulation abnormalities is ranging from clinically insignificant to development of overt DIC, associated with worse survival. Pathogen-associated molecular pattern (PAMP) activating host inflammatory response is the main trigger for coagulopathy in sepsis. Inflammatory mediators and proinflammatory cytokines such as interleukin (IL) 1, IL-6, elastase, tumor necrosis factor α (TNF-α), cathepsin G and proteins of complement system lead to activation of coagulation. Damaged cells release tissue factor (TF) which promotes procoagulant response, thrombin production and DIC, as hypercoagulable state starts. At the end of process is the consumption of all clotting factors and hypocoagulability (15). It is critically important for the clinician to understand how the ongoing pathophysiological progression of sepsis affects coagulation system, in order to deliver an appropriate therapy. Recognized limitations of CCTs, in revealing coagulopathy in sepsis, led to increased utility of ROTEM as a point of care assay (16, 17).

One of the first studies estimated 13 patients with septic DIC who showed significant EXTEM CT prolonged in DIC group, compared to non - DIC group. These results are pointing on hypocoagulability in DIC group caused by consumption of coagulation components. A correlation between EXTEM CT and JAAM (Japanese Association for Acute Medicine) DIC was observed, with CT cut off 46.0s as a most sensitive and specific for DIC diagnosis (18). Authors suggested this could be beneficial in detecting this hemostatic disorder in only few minutes from blood sampling, instead of waiting more than an hour to collect all laboratory results needed for JAAM DIC score calculation (18). Further studies performed on septic patients observed similar results: EXTEM and FIBTEM CT prolongation, and decreased EXTEM and FIBTEM MCF, as well as impaired fibrinolysis (16, 17, 19).

Prolonged CT and hyperfibrinolysis were predictors of poor prognosis (16, 17). All those results are pointing on hypocoagulability and higher bleeding risk observed in the late faze of DIC, with consumption of all clotting factors.

Novel study by Davies et al. compared septic patients in different phase: sepsis, severe sepsis and septic shock. Results suggested that patients in early stages of disease (sepsis and severe sepsis) are more likely hypercoagulable with shortened EXTEM CT, increased alpha angle and MCF. On the other hand, patients in the late stage such as septic shock more had delayed but normal clot formation with hyperfibrinolysis (LI60 in EXTEM and INTEM) and decreased clot strength (MCF in EXTEM and INTEM) (17). As in previous studies, prolonged EXTEM CT and increased LI60 were predictors of mortality.

In conclusion, hemostatic disorder in sepsis is complex, varying from hypercoagulable state in early stages to hypocoagulability in septic shock, while hypocoagulabile ROTEM pattern was a predictor for death.

ROTEM in malignancy associated coagulopathy and thrombosis

Coagulopathy in malignant disease is complex, multifactorial and yet incompletely understood. The main role in MAC is played by tumor cells and expression of procoagulant factors, soluble mediators and adhesion particles. These molecules lead to the activation of the clotting cascade, with the generation of thrombin and fibrin, and the stimulation of platelets, leukocytes and endothelial cells, which expose their cellular procoagulant features. Several of these mechanisms can contribute to tumor development and progression, particularly microparticle (MP)-enriched prothrombotic and proangiogenic factors (2, 20). According to this, venous and arterial thromboembolism (TE) might be expected complications during the course of cancer treatment, but can also be a first sign of disease. The incidence of venous TE (VTE) varies from 0.6 % to 7.8 %, while arterial TE occurs in 2-5 %, and accounts 10-30 % of all thrombotic complications in cancer patients (20, 21). Authors agree, that for TE, important role play patient-cancer characteristics, as well as treatment type. High incidences of TE in cancer patients are the reason of development risk models, based on which one could identify high-risk patient and better target thromboprophylaxis.

Clinicians have attempted to quantify the hypercoagulability in cancer patients. However, CCTs has focus on one individual point of coagulation in a specific point of time, they failed to provide a full picture of MAC. On the other hand, several studies performed on patients with intraabdominal carcinomas, gynecological and lung cancers showed ROTEM parameters could predict hypercoagulability (2, 22, 23). Results showed shortened CFT (INTEM and EXTEM), increased alpha (INTEM, EXTEM), MCF and A10/20 (INTEM, EXTEM, FIBTEM) as well as EXTEM CT are suggesting hypercoagulability (23-26). The question is how to interpret these results and could they be helpful in thromboprophylaxis decision making? An ambitious approach was given by Blasi et al. suggesting adding of ROTEM parameters as a biomarker in a risk-scoring models like Khorana risk score, in addition to traditional parameters for better stratification of patients and to better target a thromboprophylaxis (23). Despite mentioned results, consensus about the use of ROTEM in patients with MAC and interpretation of its results still has not been made.

ROTEM in hematological malignancies – yes or no?

Although patients with hematological malignancies are in a greater risk of bleeding, nowadays thrombotic complications are well recognized, and its rates similar to those observed in solid tumors with a high risk of thrombosis (20). The overall risk of VTE in patients with acute lymphoblastic leukemia (ALL) remains high at close to 10 % at 6 months from diagnosis, and the use of *L-asparaginase* increases the risk. Patients with acute myeloid leukemia (AML) have a VTE incidence of 5-8 %. High incidence of VTE (4.2 %) is observed in patients with aggressive lymphomas, while those with indolent lymphomas are at lower risk (1.4 %). The highest risk of VTE, 12 %, was observed in multiple myeloma treated with immunomodulatory agents such as thalidomide or lenalidomide. Patients not receiving these agents have VTE incidence of 5 % (27).

Today, thromboprophylaxis is based on risk models made to identify high-risk patients who could benefit from this therapy. One of widely used is already mentioned Khorana risk score (KRS), based on several predictive clinical and laboratory parameters: cancer site, platelet count, hemoglobin level or the use of erythropoiesis-stimulating agents, leukocyte count and body mass index (21). Study of KRS validation on the cohort of patients with lymphoid and myeloid malignancy has showed it did not adequately stratify or predict VTE events in patients at a higher risk of VTE (28, 29). This finding suggests the need for the development of a disease-specific VTE assessment model. Potential use of ROTEM could be beneficial. However, there is only one small study about ROTEM in assessment of thrombotic risk in patients with acute lymphoblastic leukemia receiving L-asparaginase. Results have shown 6 patients experienced VTE during the course of chemotherapy who had initially increased FIBTEM MCF, while during the therapy shortening of INTEM and EXTEM CT, as well as an increasement of EXTEM MCF was observed, all suggesting hypercoagulability (30). To our knowledge, there is no study about the use of ROTEM to access hypercoagulability in lymphomas and multiple myeloma. Further investigations about utility of ROTEM and eventually thromboprophylaxis according to its results will be needed in the future.

Acute promyelocytic leukemia (APL), nowadays is the most curable subtype of AML with complete remission achievements of > 90 % (31). However, the main obstacle in treatment is hemorrhagic early death (HED). Despite

very aggressive supportive therapy, according to CCTs performed daily during coagulopathy, HED rate is 5-10 % in randomized studies, while rate has been even higher in population-based studies (31, 32). Based on limited experience of our Clinic about use of ROTEM in APL patients, we noticed almost all had a fibrinogen level higher than 1.5 g/L not requiring cryoprecipitate transfusion on the onset, but extremely low FIBTEM MCF represented with a thin line suggesting fibrinogen function and polymerization are very poor. It still remains a question, would a ROTEM guided transfusion support contribute to favorable outcome.

Conclusion

ROTEM is a "whole blood" assay assessing a dynamic process of coagulation from its initiation to fibrinolysis, obtaining quick results. Both hypocoagulability and hypercoagulability can be detected by the use of this test, and based on its cut off values it is possible to manage transfusion support. According to mentioned characteristics, ROTEM has advantages over CCTs in trauma patients and in major surgeries, while its benefit in other fields like sepsis or DIC are still in question. Further studies will be needed to determine if ROTEM could possibly be useful as surrogate in detecting patient with malignancy in high risk of VTE. Undoubtedly, viscoelastic assays will be increasingly used in the close future.

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