Management of Trauma Induced Coagulopathy with Thrombelastography

Eduardo Gonzalez M.D.,¹ Ernest E. Moore M.D.,^{1,2} Hunter B. Moore M.D.,¹

¹ Department of Surgery - University of Colorado, Denver, CO, USA.

² Department of Surgery - Denver Health Medical Center, Denver, CO, USA.

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Correspondence:

Ernest E. Moore, MD
Editor - Journal of Trauma and Acute Care Surgery
655 Broadway, Ste. 365
Denver, CO, USA. 80203
ernest.moore@dhha.org
phone: 303-602-1820, fax: 303-602-1817

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INTRODUCTION

Contemporary trauma care comprises advanced pre-hospital care, regionalized trauma systems, damage control operative techniques, advanced critical care, rehabilitation with reintegration into society, and injury prevention.^{1,2} Despite these efforts, deaths from injury have increased in the United States over the last decade relative to other causes of mortality.^{3,4} Looking forward, in order to make strides in trauma outcomes this high mortality of severe injuries must be mitigated.

Injury mortality was classically described as having a trimodal distribution with immediate deaths at the scene, early deaths due to hemorrhage, and late deaths due to organ dysfunction; reported by Trunkey et al. in 1983.⁵ Damage control surgery and advances in critical care have decreased the incidence and severity of organ dysfunction after injury,^{6,7} while it is arguable that immediate deaths at the scene can only be addressed through injury prevention. Thus, deaths due to hemorrhage continue to represent a target for intervention in order to mitigate mortality from severe injuries. Recent studies analyzing the time course of hemorrhage related mortality report that these deaths occur despite ongoing therapies of resuscitation.⁸ Such data calls for a paradigm shift in the resuscitation of patients with injury related hemorrhage.

Resuscitation from hemorrhage is compounded by dysfunctional hemostasis seen in severely injured patients,^{9,10} hindering the effectiveness of resuscitation as well as damage and bleeding control surgery if patients are not resuscitated from this

coagulopathy. Thus, in the severely injured patient hemodynamic and hemostatic resuscitation go hand in hand. Furthermore, experimental and clinical data exists to suggest that some of our current resuscitation strategies, particularly the use of crystalloid and colloid fluids, may in fact exacerbate coagulopathy and further worsen bleeding.¹¹⁻¹⁵

In this context, viscoelastic assays such as thrombelastography (TEG) and rotational thrombelastometry (ROTEM) have emerged as point of care tools that can guide the hemostatic resuscitation of bleeding injured patients.¹⁶ These assays provide information about patients' coagulation status, which paired with other point of care available assays such as hemoglobin and blood gas enable the clinician with early management-driving data in the trauma bay. Furthermore, TEG and ROTEM assessments can be continued in the point of care mode into patients' anesthesia course in the operating room and during resuscitation and recovery in the critical care unit. Recently, a randomized clinical trial demonstrated that the use of TEG to guide a massive transfusion protocol in trauma patients, compared to conventional coagulation assays (i.e., international normalized ratio of prothrombin time [PT/INR], partial thromboplastin time [PTT], fibrinogen level, platelet count), resulted in a statistically significant decrease in mortality while using less plasma and platelet blood products.¹⁷

This article describes the role of TEG in contemporary trauma care by explaining this assays' methodology, clinical applications, and result interpretation through description of supporting studies in order to provide the reader with an evidence based user's guide. Although TEG and ROTEM are assays based on the same viscoelastic principle, this

article is focused on data supporting the use of TEG in trauma, as it is available in trauma centers in North America; ROTEM is mostly available in Europe.

HISTORICAL CONTEXT

Hellmut Hartert conceived TEG in Germany, at the Heidelberg University School of Medicine in 1948.¹⁸ TEG was applied increasingly throughout Europe during the 1950s, validating its use for assessment of anticoagulant effect, effect of thrombocytopenia, fibrinolysis, and monitoring of coagulation during liver transplantation.^{19,20} The first report on the use of TEG outside of Europe came from Henry Swan at the University of Colorado, who in 1958 published on the use of TEG to characterize the effects of hypothermia and cardiopulmonary bypass during cardiac surgery.²¹ Subsequently, Thomas Starzl utilized TEG to detect fibrinolysis during the anhepatic phase of liver transplantation.^{22,23} It gained further applicability for monitoring heparinization during cardiopulmonary bypass and was also found beneficial for predicting post-operative bleeding.²⁴ TEG gained additional acceptance as a tool for assessment of coagulation in the general surgical patient, permitting differentiation of coagulopathy from surgical bleeding.²⁵

ASSAY METHODOLOGY

The first descriptions on the methodology of this assay refer to TEG as “Hartert’s instrument”.²⁰ The principles on which TEG is currently based remain the same since then. In the current TEG system (Analyzer 5000; Haemonetics, Braintree, MA), a cylindrical plastic cup containing a 360 microliters whole blood sample oscillates through 4°45’ (0.1 Hertz) and a pin on a torsion wire is suspended in the blood (Figure 1). Initially, movement of the cuvette does not affect the pin, but as the clot develops, resistance from the developing fibrin strands couples the pin to the motion of the cuvette. As the viscoelastic strength of the clot increases more rotation torque is transmitted to the torsion wire and detected by an electromagnetic transducer. The transducer signal is then interpreted by TEG software, which represents such changes as the characteristic TEG tracing. The first iteration of TEG used a light beam paired to the pin in motion; movement of the light beam was optically recorded through a visible scale on a roll film. The distance between the lines represents the degree of firmness with which the cup is bound to the pin. If the clot subsequently undergoes lysis, this is recorded as a decrease in amplitude, consequently decreasing the distance between the lines. These changes in amplitude are plotted as a function of time. The current instrument allows near real time data gathering with most results available between 10 and 30 minutes after blood draw. Most institutions transmit a “live” TEG tracing to the emergency department trauma bay and operating room via computer, enabling prompt interpretation for goal-directed therapy.

TEG analysis can be performed on whole blood with no anticoagulant (native), whole blood collected into sodium citrate 3.2% (0.109 mol/L) (9 volumes blood to 1 volume

anticoagulant) and whole blood collected into heparin (>14.5 IU heparin/milliliter of blood sample). There has been growing interest in the effects of citrate on thrombelastographic profiles, and whether citrate can introduce variation to interpretation of results. Studies on healthy volunteers performing serial TEG assays at different time points from collection show that citrated samples produce variable results when the assay is performed within 5 minutes from sample collection but stabilize thereafter for up to 2 hours.²⁶⁻²⁹

The first step in preparing a sample to execute a TEG assay is identifying the method of collection; i.e., whether the sample is anticoagulated or not. For samples collected with no anticoagulant, the assay must be performed, ideally, as soon as possible, and recommended within 4 minutes from sample collection. For samples collected in citrate, the assay must be performed between 5 minutes to 2 hours from collection. Most centers adopt a 30 minute time from collection for citrated samples; this standardizes practice and allows for logistics of transportation and quality control of instruments. However, data has demonstrated no changes in coagulation profiles when performed as early as 5 minutes from collection,^{26,30} allowing for the use of citrated samples when TEG is performed at point-of-care in trauma settings. Citrated samples are re-calcified immediately prior to assay initiation. This is done by placing 20 microliters of calcium chloride (0.2 M) into the plastic TEG cup followed by addition of the whole blood sample. The instrument can be adjusted to match the patient's core temperature, which is useful during cardiopulmonary bypass and intraoperative protective hypothermia. Some clinicians, in situations such as trauma, prefer to run the assay at the ideal temperature of

37 degrees, in order to assess the hemostasis at the goal temperature to which the patient will be resuscitated.

ASSAY INTERPRETATION

Based on time-resistance associations, the following TEG variables are obtained: R-time, activated clotting time (ACT), K-time, angle, maximum amplitude (MA), lysis at 30 minutes (LY30). Of note, the TEG variables that have been clinically validated and are routinely used in clinical practice are: R-time, ACT, angle, MA and LY30; other variables are mostly used for research purposes. A characteristic TEG tracing is shown in Figure 2. A summary of the most commonly used TEG variables is shown in Table 1.

R-time

R, the reaction time (or gelation time) represents the latent period from the beginning of the TEG assay to the establishment of a three-dimensional fibrin gel network with measurable rigidity of amplitude of 2 mm. This variable has also been referred to as the clot initiation time. R-time is measured in minutes and has been suggested to be analogous to PT/INR and PTT, although results are not interchangeable. R-time reflects coagulation factor activity. Nielsen et al.³¹ performed a study performing TEG on plasma with specific coagulation factor deficiencies (II, VII, X, XII). Of all TEG variables analyzed, R-time was the most affected by these deficiencies. In a study performed in severe hemophiliacs receiving recombinant factor VIII prophylaxis for bleeding, TEG and a thrombin generation assay were performed in order to characterize the viscoelastic response of hemophiliac blood to factor VIII. Both TEG R-time and log

thrombin generation velocity demonstrated a strong correlation with factor VIII activity; $R = -0.81$, $p=0.001$, and $R = -0.90$, $p=0.001$, respectively. R-time is currently used in clinical algorithms and protocols to trigger plasma transfusion.³²

ACT

ACT is a variable that is exclusive to the Rapid-TEG assay. Due to the rapidity of clotting in Rapid-TEG, the R-time (expressed in minutes) is extremely small, and the range is very narrow. Because of this, an ACT time is derived in seconds, providing a broader range that allows for defining normal and abnormal values.³³ ACT and R-time are thought to represent the same phase of hemostasis. Cotton et al.³⁴ performed a prospective observational study in 583 consecutive trauma patients (median injury severity score [ISS] = 14) using Rapid-TEG upon arrival. ACT had a significant correlation with INR and PTT; $R=0.71$ and 0.75 respectively. Linear regression demonstrated that ACT predicted red blood cell, plasma, and platelet transfusions within the first 2 hours of arrival. Controlling for demographics and arrival vital signs, an ACT >128 seconds predicted massive transfusion (≥ 10 blood product units in the first 6 hours); odds ratio: 5.1 (95% CI, 1.3 –19.4). In addition, an ACT <105 seconds predicted patients who did not receive any transfusions in the first 24 hours; odds ratio: 2.80 (CI, 1.02–7.07). A recent study from our group has demonstrated that in trauma patients, an ACT >140 seconds can predict the angle and MA being abnormal.³³ Correspondingly, patients with an ACT >140 seconds required more cryoprecipitate and platelet transfusions. Thus, an ACT being available within 5 minutes allows for early delivery of cryoprecipitate and platelets units to the bedside based solely on ACT, before angle and MA are reported.

This strategy has been adopted at our institution. ACT is currently used in clinical algorithms and protocols to trigger plasma transfusion.

K-time

The K time is a measurement of the time interval from the R-time (2 mm tracing amplitude) to the point where fibrin cross-linking provides enough clot resistance to produce a 20-mm amplitude reading. It is thought to represent the propagation phase of enzymatic factors resulting in clot strengthening; which in this phase of clotting is mostly achieved by fibrinogen cleavage and fibrin polymerization. K-time occurs in the same time interval as angle (described below), which has replaced K-time in clinical practice. One of the reasons for this is that the calculation of K-time requires the TEG tracing to reach 20 millimeters of amplitude; in cases of severe coagulopathy this amplitude may not be reached and a K-time cannot be calculated. Consequently, most clinical algorithms and protocols do not use K-time to guide therapy.

Angle

This variable is the amount of degrees of the angle of a tangent line drawn between the initial split point of the tracing and the growing TEG curve. It is thought to represent the propagation phase of enzymatic factors resulting in clot strengthening; which in this phase of clotting is mostly achieved by fibrinogen cleavage and fibrin polymerization. A lower angle represents a decreased rate of clot strength growth, while a higher angle represents a greater rate of clot strength growth. Clinically, angle is used as a marker of fibrinogen concentration and function and correlates well with the specialized

TEG assay functional fibrinogen TEG (TEG-FF) ($R = 0.7$ [$p < 0.0001$]).³⁵ Angle is currently used in clinical algorithms and protocols to trigger fibrinogen replacement in the way of cryoprecipitate or fibrinogen concentrate.³⁶

MA

Maximal amplitude is the greatest strength achieved by the clot, which on the TEG tracing is represented as the width in millimeters of the widest gap in TEG tracing. MA assesses the combination of platelet count and function as well as fibrinogen activity (cleavage in to fibrin and polymerization). Kang et al.²² studied patients undergoing liver transplantation and used linear regression to evaluate the relationship between TEG variables and PT, PTT, platelet count, factors I, II, V, VII, VIII, IX, X, XI, and XII. In this study, *MA* correlated with platelet count ($r = 0.59$, $p < 0.001$) and fibrinogen level ($r = 0.64$, $p < 0.001$). The relationship of platelet count and MA was further investigated by measuring the MA and platelet count following infusion of platelets. Ten units of platelets led to an increment of $40 (\pm 31) \times 10^9/L$ in platelet count and an increase in MA of 13.2 millimeters. Interestingly, another study reported that the association between MA and platelet count becomes linear when the platelet count was $< 100 \times 10^9/L$.³⁷ However, it is important to underscore that platelet count does not necessarily correlate with platelet function, particularly, in pathologic conditions such as hemorrhagic shock. As a measure of the maximal amplitude of strength reached by the clot, MA reflects all factors that contribute to clot strength, which is mostly represented by fibrin-platelet interactions. Functional fibrinogen TEG studies in healthy volunteers have demonstrated that approximately 20% of the clot strength (MA) is determined by fibrin, with the

remaining 80% attributable to platelets. In trauma, studied upon admission, the contribution of fibrinogen to total clot strength is approximately 30%.^{35,38} Thus, MA should be interpreted as a function of interactions between these two factors, and not a sole reflection of platelet function.³⁹ MA is currently used in clinical algorithms and protocols to trigger platelet transfusion.

Shear elastic modulus strength (G)

Since MA reflects the modulus of clot strength, yet it is expressed as the amplitude of the tracing, a physical translation into an output of viscoelastic strength has been derived from MA. This variable is known as G, represents the shear elastic modulus strength, and is expressed in dynes per square centimeter. G is calculated as follows:

$$G = (5000 \times MA) / (100 - MA)$$

G is a parametric measure of clot strength. The relationship between MA and G is not linear but curvilinear – MA can vary from 0 to 100, while G varies from 0 to infinity. As it is expressed in units of strength, G facilitates interpreting clot strength as a viscoelastic variable. This relationship has lead investigators to believe that compared to G, MA may underestimate the changes in thrombus resistance characteristics. For example, when a clot with an MA of 35 millimeters is compared to another with amplitude of 70 millimeters, the difference in strength between the clots in terms of dyne/cm (G) is not 2-fold but rather 4-fold. The G variable is used is mostly for research.

LY30

LY30 is the standard measure of fibrinolysis by TEG. LY30 is determined by calculating the percent reduction of clot strength (amplitude) 30 minutes after reaching MA. Per the manufacturer, an LY30 $>7.5\%$ (i.e., 7.5% clot strength reduction between MA and amplitude 30 minutes after reaching MA) is considered abnormal. Two recent studies have investigated the ideal threshold of LY30 in trauma patients. Our group prospectively studied 73 trauma patients meeting criteria for massive transfusion protocol activation with citrated Kaolin-TEG on admission. Those patients with an LY30 $\geq 3\%$ were more likely to require a massive transfusion (90.9% vs. 30.5%, $p = 0.0008$) and to die from hemorrhage (45.5% vs. 4.8%, $p = 0.0014$) compared to those with an LY30 $<3\%$. In a similar study performed using citrated Rapid-TEG, Cotton et al.¹² found that the LY30 value associated with a significant increase in mortality was $\geq 3\%$. The odds of mortality increased 10-fold when an LY30 $\geq 3\%$ was reached. These authors called for reconsideration of the LY30 threshold given that the normal reference range had been considered to be 0.0% to 7.5%. It has been speculated that the use of a citrated sample and an activator (kaolin or tissue factor) can yield different LY30 sensitivities among TEG assays. Our group investigated this by performing a study on healthy control blood samples in which tissue plasminogen activator (tPA) was used to induce fibrinolysis in-vitro and head to head citrated Kaolin, native Rapid and native TEG (non-citrated) were performed.⁴⁰ Citrated native TEG to detected fibrinolysis by LY30 earlier and to a greater degree. This finding remains to be validated in coagulopathic trauma patients with fibrinolysis; however, a citrated native TEG should be considered the assay of choice for detecting fibrinolysis in experimental models and is the assay modality currently used in

the newly developed tPA challenge TEG. Furthermore, our group has recently reported data demonstrating that in trauma patients, an LY30 approximating 0 is abnormal. We studied trauma patients with an ISS >15 by stratifying this cohort by the degree of fibrinolysis (LY30) evident upon arrival.⁴¹ Sixty four percent of patients had an LY30 <0.8 (referred to as fibrinolysis shutdown), which was associated with a greater mortality rate (26%) compared to patients with an intermediate degree (LY30 0.8-3.0%) of fibrinolysis (5% mortality) (p=0.001). These data suggests that in trauma patients, the degree of normal fibrinolysis (i.e., physiologic fibrinolysis associated with the least mortality) is in the range of 0.8 to 3.0% LY30, in contrast to the 0 to 7.5% range reported by the manufacturer.

Reference Ranges

While reference ranges based on multi-institutional studies have been published for TEG, recent proficiency data indicates very large inter-institutional variation in results; coefficients of variation of up to 80%.⁴² This is thought to be due to age related changes and variations in phenotypes of hemostasis seen across populations, as well as instrument operator variability. Thus, generic reference ranges may not be applicable to individual centers and should be locally produced. Reference ranges for the most commonly used TEG assays, Rapid-TEG and Kaolin-TEG, are shown in Table 2 as reported by the manufacturer. Our group recently conducted a comprehensive analysis of TEG in 160 healthy volunteers in Denver in order to validate and standardize normal ranges of TEG. Results from this study are summarized in Table 3.

Given that these reference ranges represent coagulation in a healthy state and may not reflect unique pathophysiological aspects only seen once trauma induced coagulopathy (TIC) ensues, our group recently studied 190 severely injured patients at risk for TIC upon presentation in order to clinically validate parameters for goal-directed treatment.⁴³ By performing an optimal cut-point analysis on these data the parameters for the TEG variables depicted in Figure 3 were derived.

ROTEM

Thromboelastometry (ROTEM) is another viscoelastic coagulation test that provides a more comprehensive and dynamic overview of individual patient coagulation compared to standard coagulation testing. ROTEM, like TEG, also provides information on the speed of coagulation initiation, kinetics of clot growth, clot strength and breakdown of the clot. The ROTEM device uses a plastic pin immersed vertically into a cup containing the patient blood sample. The pin is rotated slowly through an angle of 4.75 degrees. Four tests are performed simultaneously: INTEM (intrinsic activation), EXTEM (extrinsic activation), FIBTEM (fibrin component of the clot) and APTEM (aprotinin; fibrinolysis inhibitor used with EXTEM). ROTEM, like TEG, has also been used to guide early and individualized goal-directed therapy for trauma-induced coagulopathy. A number of institutions have ROTEM-based algorithms (Figure 4) for management of acute hemorrhage and coagulation disorders in trauma patients.

LIMITATIONS OF VISCOELASTIC ASSAYS

Understanding the limitations of viscoelastic assays is essential for adequate clinical implementation and therapy guidance. First, these assays do not reflect most interactions occurring between the fluid phase of coagulation and the endothelial cell surface; this dynamic is clearly present in the coagulopathic patient; however, it remains to be understood. Second, platelet inhibition/dysfunction may not be evident with the standard assays, unless thrombin is inhibited and platelet agonists are utilized in the specialized TEG platelet mapping assay.¹⁶ Third, TEG and results are currently operator dependent and subject to sampling and/or processing errors, as well as inter-sampling variability. A newer generation of the TEG analyzer currently in development may obviate these issues.

TEG IN TRAUMA INDUCED COAGULOPATHY

Until a decade ago, the diagnosis of TIC was made with conventional coagulation tests such as PT/INR. It is important to recognize that PT/INR and PTT were initially developed for the screening of heritable coagulopathies such as hemophilia, and subsequently used to monitor anticoagulant therapy.⁴⁴ The end point for these tests is the time, in seconds, until the earliest formation of fibrin is detected. These assays do not assess the evolution of the clot beyond the formation of the first strands of fibrin. Furthermore, they have shown to correlate poorly with bleeding risk in elective general and vascular surgeries.⁴⁵ As classic coagulation tests have shortcomings when used to diagnose and monitor coagulopathy in the trauma patient, viscoelastic assays such as TEG have emerged in the last decade as a novel application of a well-established technology.

TEG was first used in trauma patients during the late 1990's as a research tool to

characterize changes in the different stages of hemostasis during TIC.⁴⁶ It wasn't until a decade after that the first reports on standardized management strategies of TIC using TEG were published by our group and others.⁴⁷⁻⁴⁹

The greatest clinical application of TEG in trauma is in the guidance of massive transfusion protocols (MTP). Until recently, the ideal strategy to guide MTP in injured patients remained elusive. In 2013 Tapia, Mattox et al.⁵⁰ published a study comparing their TEG-guided MTP to a historical cohort in which MTP was carried out using a fixed transfusion ratio of 1:1:1 red blood cell to plasma to platelet units. Patients studied were transfused 6 or more units of red blood cells in the first 24 hours from arrival. The median ISS of patients ranged from 23 to 29 and was not significantly different between the groups compared. These authors found that patients with penetrating trauma that had an MTP guided by TEG had improved mortality compared to the fixed ratio MTP historic cohort. Our group recently published a randomized clinical trial in which patients were randomized to either a MTP guided by TEG or conventional coagulation assays (CCA) (e.g., INR, PTT, platelet count, fibrinogen, d-dimer).¹⁷ A total of 111 patients were enrolled with median ISS of 30 and 27% had a penetrating injury mechanism. The TEG guided MTP group had a survival advantage over the CCA group; mortality of 19% in the TEG group compared to 36% in the CCA group ($p=0.04$); hazards ratio of mortality in the CCA group of 2.1 (95% CI: 1.02-4.45). The difference in mortality was attributed to less early hemorrhagic deaths in the TEG group. More plasma and platelet units were transfused to the CCA group in the first two hours from arrival, while more cryoprecipitate was transfused overall to the CCA group. There were no differences in the timing and amount of crystalloid and red blood cell units administered. This finding

suggests that TEG allows for more appropriate hemostatic blood product use. Patients in the TEG group also had more ventilator-free and intensive care unit (ICU) -free days, which is potentially related to appropriateness of blood product administration. Our Institution's goal-directed TEG-guided MTP is shown in Figure 3.

TEG has also allowed for characterization of distinct phenotypes of TIC, indicating that the pathophysiological mechanisms of TIC maybe different based on patient characteristics, co-morbidities, and injury patterns. Our group performed a principal component analysis (PCA) on TEG variables of severely injured patients (median ISS of 31).⁵¹ PCA identified three principal components that together explained 93% of the overall variance. The first phenotype reflected global coagulopathy with depletion of platelets and fibrinogen, a second group consisted of fibrinolysis as the main driver of TIC. Kutcher and Cohen et al.⁵² from the San Francisco group performed a similar study applying PCA to coagulation factor activity. These authors also reported two principal component groups; the first one consisting of global clotting factor depletion and a second one characterized by activation of protein C and hyperfibrinolysis. These data suggest that trauma patients present with different pathophysiological drivers of coagulopathy and underscore the importance of personalized resuscitation of TIC.

Clinical studies have identified that in those coagulopathic patients with the highest hemorrhage related mortality fibrinolysis is a conspicuous factor.^{41,53,54} Thus, treating fibrinolysis with anti-fibrinolytic medication poses a potential strategy to improve outcomes of trauma patients. However, controversy exists regarding the threshold for administering this medication and potential adverse effects. Although the CRASH-2 trial reported a 1.5% benefit in mortality when the anti-fibrinolytic tranexamic

acid was administered empirically to all trauma patients,⁵⁵ there has been significant criticism regarding the clinical applicability of this study's findings.⁵⁶ This trial did not perform any coagulation assays to either demonstrate the patients' degree of coagulopathy and fibrinolysis or to characterize the effect of the drug. Importantly, this study also found that administration of tranexamic acid >3 hours after injury was associated with increased mortality; the study did not report any causality or mechanism to explain this finding. It seems intuitive that an anti-fibrinolytic medication (e.g., tranexamic acid) should only be administered to those who have demonstrable hyperfibrinolysis; however, advocates for its empiric administration to all trauma patients still exist. TEG is the only clinically available assay that can detect fibrinolysis accurately and in a point of care setting. Several studies have demonstrated an association of hyperfibrinolysis detected by TEG with increased mortality and need for massive transfusion.^{12,41,57} Furthermore, with the recent characterization of fibrinolysis shutdown,⁴¹ present in 63% of severely injured patients on arrival, administration of an anti-fibrinolytic to these patients should be avoided. Our institution's approach to hyperfibrinolysis is goal-directed,³² just as it is for transfusion of hemostatic blood products, administering tranexamic acid only to those patients who have an LY30 >3-5%.

CONCLUSION

Viscoelastic assays such as TEG are the coagulation tests that better represent TIC and enable the clinician with data for critical decision making. TEG's greatest application in trauma care is in the guidance of massive transfusion protocols. In summary, the insights into TIC that TEG has provided, both from the clinical and biological mechanism

standpoint, are substantial, and pose an opportunity for further investigations.

TABLE 1. TEG variables most commonly used in clinical practice.

TEG variable	Significance	Unit of measure
R-time	Time elapsed from the initiation of the test until the point where the onset of clotting provides enough resistance to produce a 2 mm amplitude reading on the TEG tracing.	minutes
ACT	Used as a surrogate of R-time in the Rapid-TEG assay, which uses tissue factor to obtain a quicker reading.	seconds
Angle	Angle of a tangent line between the initial split point of the tracing and the growing curve. Reflects potentiation phase of enzymatic factors yielding clot strengthening mostly derived from fibrinogen cleavage and fibrin polymerization.	degrees
MA	Point at which clot strength reaches its maximum measure in millimeters on the TEG tracing; reflects the end result of maximal platelet–fibrin interactions.	millimeters
LY30	Percentage of clot strength amplitude lost 30 minutes after reaching maximal amplitude; reflects amount of fibrinolysis.	percent
TEG: thrombelastography; R-time: reaction time; ACT: activated clotting time; MA: maximum amplitude; LY-30: lysis at 30 minutes.		

TABLE 2. Manufacturer reference ranges of TEG variables for the two most commonly used TEG assays in clinical practice: Rapid-TEG and Kaolin-TEG.

TEG assay	Sample collection		TEG variable			
		ACT (seconds)	R-time (minutes)	angle (degrees)	MA (millimeters)	LY30
Kaolin	non-citrated	N/A	4 – 9	59 – 74	55 – 74	0 – 7.5%
	citrated		5 – 10	53 – 72	50 – 70	0 – 7.5%
Rapid	non-citrated	78 – 110	N/A	66 – 82	54 – 72	0 – 7.5%
	citrated	86 – 118		64 – 80	52 – 71	0 – 7.5%
TEG: thrombelastography; R-time: reaction time; MA: maximum amplitude; LY30: percent lysis 30 minutes after reaching MA.						

TABLE 3. Range of TEG variables from healthy control study (N=160) performed in Denver. Range determined by ± 2 standard deviations from the mean.

TEG assay	Sample collection		TEG parameter			
		ACT (seconds)	R-time (minutes)	angle (degrees)	MA (millimeters)	LY30
Native	non-citrated	N/A	8 – 12	12 – 34	39 – 60	1.6 – 5%
	citrated		9 – 17	26 – 61	44 – 67	1.8 – 5%
Kaolin	non-citrated	N/A	4 – 11	53 – 75	56 – 75	0.7 – 5%
	citrated		6 – 12	49 – 69	54 – 71	0.9 – 5%
Rapid	non-citrated	78 – 146	N/A	66 – 81	56 – 74	0.2 – 5%
	citrated	91 – 140		62 – 81	53 – 71	0.1 – 5%
TEG: thrombelastography; R-time: reaction time; MA: maximum amplitude; LY30: percent lysis 30 minutes after reaching MA.						

Figure 1.

Figure 2.

Figure 3.

Figure 4.

ROTEM® Results in Clinically Significant Bleeding		
CT _{IN}	Prolonged	Suggests Heparin influence or intrinsic factor deficiency
CT _{EX}	Prolonged	Suggests extrinsic factor deficiency
A10 _{IN, EX}	Reduced	Suggests poor clot firmness as a result of decreased: Platelets, fibrinogen and/or FXIII
MCF _{IN, EX}	Reduced	Suggests poor clot firmness as a result of decreased: Platelets, fibrinogen and/or FXIII
MCF _{FIB}	Reduced	Suggests poor fibrin contribution to clot firmness
ML _{IN, EX, FIB}	> 15%	Suggests hyperfibrinolysis

FIGURE LEGENDS

Figure 1. TEG cup and pin design.

Courtesy of the Haemoscope Corp, Niles, IL.

Figure 2. Characteristic TEG tracing. R: reaction time (R-time); K: coagulation time (K-time); MA: maximum amplitude; LY30: percent reduction in amplitude 30 minutes after reaching MA.

* For the Rapid-TEG assay, R-time is replaced by ACT.

Adapted from Trapani, L. Thromboelastography: Current Applications, Future Directions *Open Journal of Anesthesiology* (2013), 3:1, 23-27; with permission.

Figure 3. Denver Health Medical Center Goal-directed Massive Transfusion Protocol.

From Einersen PM ME, Chapman MP, Moore HB, Gonzalez E, Silliman CC, Banerjee A, Sauaia A. Rapid-thromboelastography (r-TEG) thresholds for goal-directed resuscitation of patients at risk for massive transfusion. *Journal of Trauma and Acute Care Surgery*; with permission.

Figure 4. ROTEM-guided treatment algorithm for managing trauma-induced coagulopathy and diffuse microvascular bleeding (AUVA Trauma Hospital, Salzburg, Austria). The algorithm represents standard operating procedure for ROTEM-guided haemostatic therapy upon admission of trauma patients to the emergency room.

From Schöchl H, Maegele M, Solomon C, Görlinger K, Voelckel W. Early and individualized goal-directed therapy for trauma-induced coagulopathy. *Scand J Trauma Resusc Emerg Med*. 2012 Feb 24;20:15; with permission.

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