



# Viscoelastic Hemostatic Tests and Fibrinogen Concentrations in Trauma

# 14

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## Abstract

Thrombelastography (TEG) and rotational thromboelastometry (ROTEM) are used to diagnose trauma-induced coagulopathy, fibrinogen deficiency, and guide fibrinogen transfusion in trauma, as well as to study the hemostatic effect of fibrinogen supplementation. We reviewed the clinical applications of TEG and ROTEM focusing on two functional fibrinogen (FF) tests, TEG FF and ROTEM FIBTEM, for assessing and guiding fibrinogen replacement in trauma patients. ROTEM FIBTEM, the standard FF test, measures clot amplitude. In contrast,

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while TEG FF, which is considered the standard FF test, also measures clot amplitude, other TEG tests, e.g., kaolin and rapid TEG, measure several coagulation parameters (maximum amplitude, K value, and angle  $\alpha$ ) to assess FF. Some confounding factors (e.g., hematocrit, factor XIII, and resuscitation fluids) need to be considered when interpreting the hemostatic effect of fibrinogen replacement measured by TEG and ROTEM. Different cutoff values for TEG and ROTEM parameters, particularly for maximum clot firmness (MCF) in FIBTEM, have been used for fibrinogen replacement. The dosage of fibrinogen replacement can be calculated based on the desired increment in the FIBTEM MCF or plasma fibrinogen level. In addition, we compared the clinical performance of the two FF test systems; the results were correlated but not interchangeable.

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### Keywords

Coagulopathy · Hemorrhage · Hypofibrinogenemia · Fibrinogen · Rotational thromboelastometry · ROTEM · Thrombelastography · TEG · Trauma · Viscoelastic tests · Conventional coagulation tests

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### Abbreviations

ACT	Activated clotting time
CAs	Clot amplitudes
CCTs	Conventional coagulation tests
CFT	Clot formation time
CL30	Clot amplitude at 30 min after MA relative to MA
CT	Coagulation time
ELISA	Enzyme-linked immunosorbent assay
FC	Fibrinogen concentrate
FF	Functional fibrinogen
FFP	Fresh frozen plasma
INR	International normalized ratio
K	Kinetic time
LI30	Lysis index at 30 min after CT
LY30	Clot lysis at 30 min after MA
MA	Maximum amplitude
MCF	Maximum clot firmness
PT	Prothrombin time
PTT	Partial thromboplastin time
R	Reaction time
RBC	Red blood cells
ROTEM	Rotational thromboelastometry
SLT	Standard laboratory test
TEG	Thrombelastography
TIC	Trauma-induced coagulopathy

## Introduction

Hemorrhage is the leading cause of preventable death in combat trauma (Eastridge et al. 2012) and secondary cause of death in civilian trauma (U. S. Burden of Disease Collaborators 2013). Coagulopathic bleeding is frequently present (at least one quarter of civilian trauma patients and one third of military trauma patients present with a laboratory-defined coagulopathy) early after major trauma (Chang et al. 2016) and causes a three- to five-fold increase in mortality (Hess et al. 2008; Davenport and Brohi 2015). Nearly one third of severe trauma patients present with trauma-induced coagulopathy (TIC) which carries a 50% mortality rate (Maegele et al. 2012; Simmons et al. 2014). The degree of TIC worsens as the injury severity increases (Cohen and West 2011; Frith et al. 2010). Therefore, early diagnosis, prevention, and treatment of TIC in the prehospital setting and at admission are of major interest in trauma patients.

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## Viscoelastic Hemostatic Tests

Thrombelastography (TEG; Haemonetics Corporation, Haemoscope Division, Nile, Illinois, USA) and rotational thromboelastometry (ROTEM; Tem Innovations GmbH, Munich, Germany succeeded by Instrumentation Laboratory, Bedford, Massachusetts, USA) are two point-of-care systems for hemostatic tests in whole blood (Whiting and DiNardo 2014). Both provide a global measure of hemostasis by quantitatively measuring the elasticity of blood from the beginning of coagulation to the ending with fibrinolysis. This includes the onset of clot formation, its progress, maximum clot strength, and clot stability, which provides important information about coagulation, fibrinolysis, and platelet function (Luddington 2005). TEG and ROTEM can also identify the relative contributions of clotting factors, such as fibrinogen and platelets, to the overall coagulation process (Whiting and DiNardo 2014).

TEG and ROTEM have been increasingly used in various clinical settings involving bleeding patients to diagnose and treat TIC (Hartmann et al. 2020a) including fibrinogen deficiency (Schlimp and Schöchel 2014), predict the risk of bleeding and mortality, and guide fibrinogen transfusion in trauma (Figueiredo et al. 2016), cardiac surgery (Görlinger et al. 2013), liver transplantation (Goerlinger 2006), and postpartum bleeding (Ranucci et al. 2016). A randomized clinical trial has concluded that TEG-guided massive transfusion protocol for severe trauma improves survival compared with that guided by conventional coagulation tests (CCTs, e.g., prothrombin time [PT]/international normalized ratio [INR], fibrinogen, and D-dimer) and utilizes less plasma and platelet transfusion during the early phase of resuscitation (Gonzalez et al. 2016). However, the latest multicenter randomized controlled trial (iTACTIC; NCT02593877) involving nearly 400 patients comparing TEG- or ROTEM-guided transfusion therapy with CCT-guided transfusion showed that the 28-day mortality was strongly reduced by TEG- or ROTEM-guided transfusion in patients with major hemorrhage who had a severe traumatic brain injury;

however, there was no difference in the proportion of patients who were alive and did not require massive transfusion at 24 h after injury (Baksaas-Aasen et al. 2021). Although the evidence on the benefit of TEG and ROTEM over CCTs in trauma is limited at this time, substantial evidence from elective cardiac and liver transplant surgery studies provides further support for the use of TEG and ROTEM (Dias et al. 2019).

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## Fibrinogen

Fibrinogen plays a central role in both primary and secondary hemostasis (Levy et al. 2012) and TIC (Schlimp and Schöchl 2014). Upon major trauma, fibrinogen reaches levels critically below the physiological level of 2–4 g/L, earlier than those of other routine coagulation parameters and before patients meet the criteria for massive blood transfusion (Schlimp and Schochl 2014; Hayakawa et al. 2015). Low fibrinogen levels are associated with increased bleeding and coagulopathy and, as a result, poor clinical outcomes (Schlimp and Schochl 2014). The fibrinogen level is an independent predictor of mortality in major trauma patients and of the requirement for massive transfusion in patients with pelvic fractures (McQuilten et al. 2017a; Notani et al. 2020).

Different cutoff values of fibrinogen concentrations ranging from 1 to 1.8 g/L were used to define hypofibrinogenemia (Peng et al. 2019; Rourke et al. 2012). The current guidelines recommend fibrinogen supplementation (with fibrinogen concentrate (FC) or cryoprecipitate) in a bleeding patient with fibrinogen levels <1.5 g/L (Kozek-Langenecker et al. 2017; Rossaint et al. 2016) or equivalent by viscoelastic testing (Černý et al. 2022).

There is, however, a paucity of evidence to support the early replacement of fibrinogen in severely injured trauma patients. A systematic review and meta-analysis of the use of FC for trauma-related bleeding found no statistically significant difference in mortality between the groups, with 22% and 23.4% in the FC and comparator arms, respectively: risk ratio 1.00 [95% confidence interval 0.39–2.56],  $p = 0.99$ . Additionally, there was no statistical difference between FC and control in packed red blood cells (RBC), fresh frozen plasma (FFP), platelet transfusion requirements, and thromboembolic events (Stabler et al. 2020). On the other hand, another recent review of 21 major randomized controlled trials assessing FC use in perioperative settings found that approximately 60% of the studies in which FC was used to treat clinically relevant bleeding showed decreased bleeding tendency and decreased transfusion requirements versus comparative treatment (Cushing and Haas 2019).

Viscoelastic functional fibrinogen tests in particular ROTEM FIBTEM have been widely used for assessment of fibrinogen deficiency, prediction for transfusion requirement, and guided fibrinogen replacement, while studies focusing on TEG functional fibrinogen (FF) are limited (Peng and Nascimento 2018). A retrospective observational study showed that the incorporation of TEG FF into TEG-based

coagulation management and FC administration reduced the need for transfusion in patients undergoing liver transplantation, with no impact on survival (Kozek-Langenecker et al. 2017; Peng and Nascimento 2018).

The review is structured into four main sections. The first section describes the principles of the two systems and various commercially available tests employing them, with an emphasis on FF tests. The similarities and differences of the two systems along with new viscoelastic testing systems are discussed as well. The second section reviews the use of TEG and ROTEM for diagnosis of TIC including TEG FF and ROTEM FIBTEM for hypofibrinogenemia. The third section depicts the use of TEG and ROTEM to assess FF levels and the hemostatic effect of fibrinogen replacement. The fourth section discusses TEG- and ROTEM-guided fibrinogen replacement.

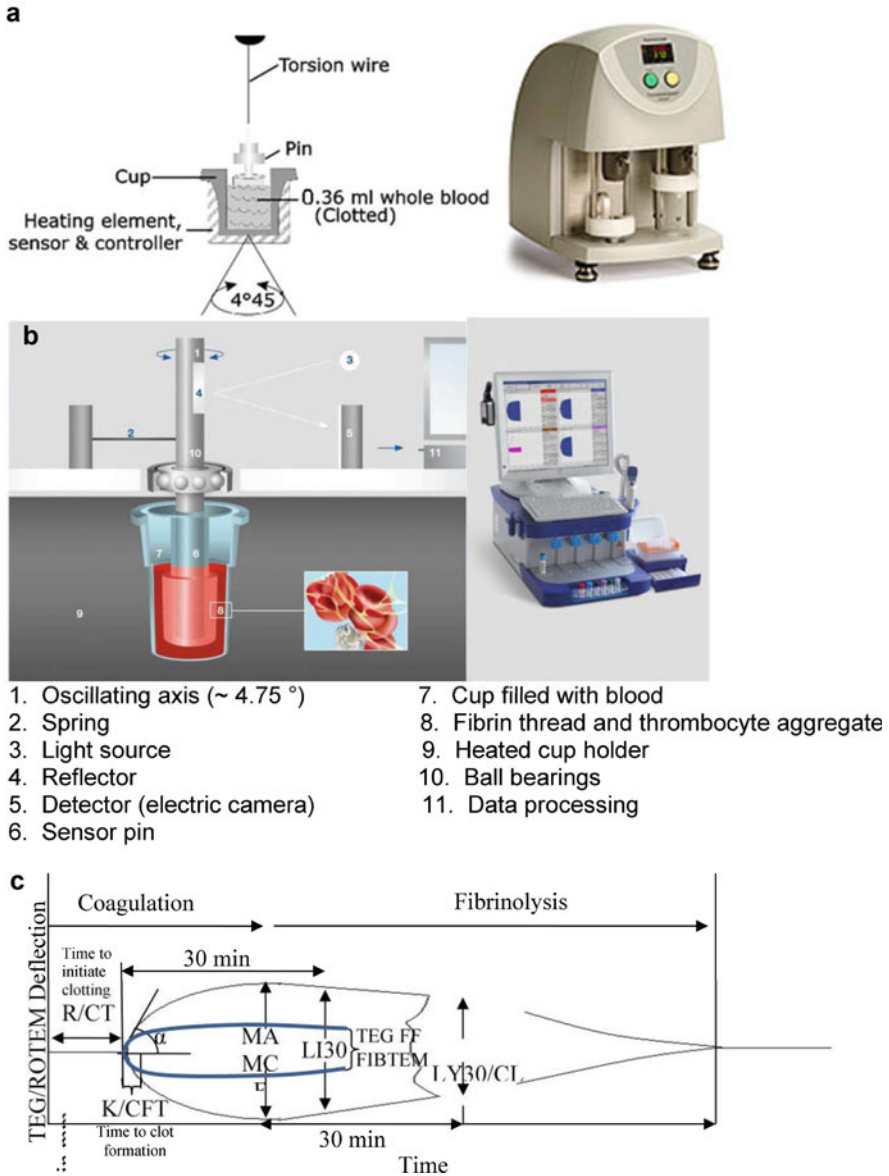
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## Principles of TEG and ROTEM FF Tests

Figure 1a and b show the testing principles of the two most commonly used systems for FF tests: the TEG 5000 Hemostasis Analyzer and the ROTEM delta system. Both systems measure the viscoelastic properties of blood as it clots under low shear stress, but there are primary hardware differences between the two, as detailed by Peng et al. (2018). Briefly, the hardware differences include the mechanisms for cup/pin rotation and the detection of the rotation, cup materials, and interior surface properties.

For both systems, measurement is graphically represented as a characteristic shape profile over time (Fig. 1c). From this graph, the following parameters can be derived for TEG: (1) the reaction time R, which is related to plasma clotting factors and circulating anticoagulants; (2) the kinetic time K, which is associated with the activities of the clotting factors, fibrinogen, and platelets; (3) the rate of clot polymerization, represented by the angle  $\alpha$ , which is a main function of the platelets, fibrinogen, and plasma components residing on the platelet surface; (4) the maximum amplitude (MA) or maximum clot strength, which is a direct function of the maximum dynamic properties of fibrin and platelet number and functions; and (5) fibrinolysis at 30 min or the rate of amplitude reduction 30 min after MA, LY30/CL30, which is related to plasma levels and activities of tissue plasminogen activator and its inhibitors. For the TEG FF test, the FF level (FLEV) in mg/dL or g/L can be calculated from MA using analytical software (Agarwal et al. 2014). For rapid TEG, in which both intrinsic and extrinsic activators are used, the activated clotting time (ACT) is calculated from the R value using the TEG software and may provide a better measure of initial clot formation than R itself (Blaine and Steurer 2019).

Similar parameters, as shown in Fig. 1c (e.g., coagulation time (CT), clot formation time (CFT), angle  $\alpha$ , MCF, and clot lysis index LI30), are measured by ROTEM. In addition, clot amplitudes (CAs) at 5 and 10 min after CT (i.e., CA5 and CA10) have been reported for ROTEM.



**Fig. 1** Principles of and instruments for two viscoelastic testing systems. Schematic illustration of the mechanism and photograph of each instrument: (a) TEG 5000 (Haemonetics Corp., Niles, IL, USA), (b) ROTEM delta (Instrumentation Laboratory, Bedford, MA, USA), and representative TEG/ROTEM tracing showing the relationship between qualitative tracing and quantitative parameters (c). Panels A and B: courtesy of Haemonetics Corp. and TEM Systems Inc.

## Comparison of TEG and ROTEM FF Tests

In addition to instrumental differences, the two abovementioned viscoelastometric systems use different reagents, as summarized in Table 1 (Whiting and DiNardo 2014; Schöchl et al. 2013a; Carroll et al. 2009; Blaine and Steurer 2019). Specifically, the FF reagent for TEG is composed of lyophilized tissue factor and a platelet inhibitor (abciximab) that binds to glycoprotein-IIb/glycoprotein-IIIa receptors to inhibit platelet aggregation and exclude platelet contribution to clot strength (Solomon et al. 2012). For the TEG FF test, 0.5 mL of citrated or native blood is activated with a mixture of tissue factor and a monoclonal glycoprotein IIb/IIIa receptor antagonist, and then 340  $\mu\text{L}$  of the activated blood is added to a TEG cup preloaded with 20  $\mu\text{L}$  of 0.2 M  $\text{CaCl}_2$  (Ferrante et al. 2016). For the ROTEM FF test (FIBTEM), 20  $\mu\text{L}$  of ex-TEM, 20  $\mu\text{L}$  of fib-TEM solution, and 300  $\mu\text{L}$  of citrated blood are mixed directly in a ROTEM cup (Solomon et al. 2012). The ex-TEM solution contains a combination of recombinant tissue factor and phospholipids that activates the extrinsic pathway of the coagulation system, whereas the fib-TEM solution contains  $\text{CaCl}_2$  as a recalcification reagent and a platelet inhibitor (cytochalasin D) that inhibits the actin/myosin system. Studies comparing different TEG and ROTEM FF tests have shown that the platelet inhibitor abciximab in TEG FF is less effective in eliminating the platelet contribution to clot strength than cytochalasin D in ROTEM FIBTEM; this results in a larger MA in TEG FF than MCF in ROTEM FIBTEM, affecting their dependence on the fibrinogen level (Solomon et al. 2012; Schlimp et al. 2014). Moreover, the TEG FF reagent does not contain heparinase or polybrene and therefore cannot be used for heparinized patients, unless a heparinase TEG cup is used. In contrast, the ROTEM FIBTEM reagent ex-TEM contains the heparin inhibitor polybrene. A new reagent, fib-TEM PLUS, containing two platelet inhibitors, cytochalasin D and tirofiban, provided the most accurate assessment of clot strength ascribed to fibrinogen function (Solomon et al. 2013a).

TEG and ROTEM have yielded different results for diagnosing coagulopathy and guiding transfusion (Sankarankutty et al. 2012), and different transfusion algorithms have been developed for each system (Coakley et al. 2006; Enriquez and Shore-Lesserson 2009). For example, ROTEM-based algorithms tended to recommend the use of FC (Schöchl et al. 2010b) or cryoprecipitate (Tanaka et al. 2012), whereas TEG-based algorithms tended to recommend the use of plasma (Coakley et al. 2006); however, both systems recommended lower transfusion than standard laboratory measures of coagulation. These differences may be due to the tests rather than the instruments, as most ROTEM-guided transfusions involve FIBTEM, which is a specific test for fibrinogen level and function (Görlinger et al. 2012), while the TEG FF test is less involved in TEG-guided transfusions (Sawyer et al. 2012) and FC administration (Levy et al. 2014; Spahn et al. 2016).

Agreements between TEG and ROTEM recommendations to transfuse platelets were fair (kappa coefficient of agreement ( $\kappa$ ) = 0.33 between ROTEM INTEM and native heparinase TEG, and  $\kappa$  = 0.28 between ROTEM INTEM and kaolin heparinase TEG) but were low in case of a low MA, suggesting the need for transfusion of either fibrinogen or platelets. There was a moderate agreement

**Table 1** Summary of TEG and ROTEM tests, their corresponding activators and inhibitors, and their applications (Whiting and DiNardo 2014; Schöchel et al. 2013a; Carroll et al. 2009; Blaine and Steurer 2019)

Type of reagents	TEG		ROTEM		Applications	Test	Applications
	Constituents	Test	Constituents	Test			
Calibration reagents	Lyophilized animal citrated plasma with stabilizers and buffers	Level 1 for normal control and level 2 for abnormal control	Quality control	Lyophilized human citrated plasma with stabilizers and buffers	ROTEC N for normal control and ROTROL P for abnormal control	Quality control	
Recalcification reagent	0.2-M CaCl <sub>2</sub> aqueous solution	Native TEG	Not often used because of long runtime and high variability	Star-TEM: 0.2 M CaCl <sub>2</sub> and 0.1% NaH <sub>2</sub> PO <sub>4</sub> in pH 7.4 buffer	NATEM	Not often used because of long runtime and high variability	
Surface activator	Kaolin suspension in a buffered stabilizer and a mixture of phospholipids	Kaolin TEG	Information similar to that of aPTT; thrombin generation as indicated by R	In-TEM: ellagic acid and partial thromboplastin phospholipid and preservatives in buffer	INTEM	Information similar to that of aPTT for intrinsic coagulation pathway; thrombin generation as indicated by CT	
Extrinsic activator	8% kaolin, human recombinant tissue factor, phospholipids, buffers, and stabilizers	Rapid TEG	Both intrinsic and extrinsic pathways are activated to more rapidly assess coagulation properties	Ex-TEM: a combination of recombinant tissue factor; polybrene, and phospholipids	EXTEM	Information similar to that of PT for extrinsic coagulation pathway, indication for FFP/PCC administration	
Platelet inhibitor	Lyophilized tissue factor and abciximab	FF TEG	Used in conjunction with kaolin TEG can assess relative contribution of	Fib-TEM: a combination of a platelet inhibitor (cytochalasin D) and CaCl <sub>2</sub> and ex-TEM	FIBTEM	Measurement of fibrinogen and platelet contribution (in conjunction with EXTEM) to clot	



Heparin inhibitor	Lyoophilized heparinase I from <i>Flavobacterium heparinum</i> at 2 IU in a TEG cup is sufficient to reverse 6 IU of heparin/mL of blood	HTEG	Compared with kaolin TEG to assess heparin effects	Hep-TEM: lyophilized heparinase I from flavobacteria, preservatives and buffer and Ca-containing diluent and start reagent with NaN <sub>3</sub> (< 0.1%) and preservatives and in-TEM	HEPTEM	Assessment of heparin effect in conjunction with INTEM
Platelet activator	AA ADP	Platelet mapping TEG	Assessment of coagulopathy, plate dysfunction, and hyperfibrinolysis and suggestion of interventions	ADP or thrombin receptor-activating peptide 6, buffers and stabilizers with ROTEM platelet module	ADPTEM TRAPTEM	Assessment of platelet function by activating either the ADP or the thrombin receptor pathway
Fibrinolysis inhibitor	Not available			Ap-TEM: aprotinin, 0.2 M CaCl <sub>2</sub> , and 0.1% NaN <sub>3</sub> in a pH -7.4 buffer and ex- TEM	APTEM	Assessment of fibrinolysis in conjunction with EXTEM, indication for tranexamic acid administration

Abbreviations: *aPTT* activated partial thromboplastin time, *Ca* calcium, *CaCl<sub>2</sub>* calcium chloride, *HTEG* kaolin TEG with heparinase, *NaN<sub>3</sub>* sodium azide, *PT* prothrombin time, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrate, *TEG* thrombelastography, *ROTEM* rotational thromboelastometry, *CT* coagulation time, *FF* functional fibrinogen, *AA* arachidonic acid, *ADP* adenosine 5'-diphosphate

between ROTEM INTEM and prothrombin time ( $\kappa = 0.42$ ) and a poor agreement between the recommendations of viscoelastic tests to administer FFP (Coakley et al. 2006). ROTEM FIBTEM has been used to assess and guide fibrinogen replacement. In contrast, TEG FF is less used for TEG-guided transfusion (Sawyer et al. 2012). There is a lack of studies directly comparing the utilities of ROTEM FIBTEM and TEG FF for the diagnosis of coagulopathies, including hypofibrinogenemia, and the guidance of transfusions, including fibrinogen replacement, although both have been reported to be useful (Carroll et al. 2009; Rugeri et al. 2007).

Meyer et al. (2014) compared different TEG and ROTEM tests, including TEG FF and FIBTEM, and the Clauss method to detect trauma-induced coagulopathy and goal-directed transfusion therapy. TEG FF and ROTEM FIBTEM early amplitudes (CA5, CA10) and MA/MCF had similar correlations with Clauss fibrinogen levels and could differentiate coagulopathic and transfused patients from non-coagulopathic and non-transfused patients. In a similar study, TEG and ROTEM were compared for FF tests in trauma patients (Meyer et al. 2015). TEG FF MA and ROTEM FIBTEM MCF correlated well with each other ( $\rho = 0.71$ ,  $p < 0.001$ ) and with the Clauss fibrinogen level ( $\rho = 0.64$  for both,  $p < 0.001$ ).

We compared the capabilities of the TEG and ROTEM FF tests to detect coagulation and fibrinolysis changes in response to hemostatic treatment and to predict acute traumatic coagulopathy and transfusion requirements in a randomized, controlled trial for fibrinogen in the initial resuscitation of severe trauma (Peng et al. 2018; Peng et al. 2019). Overall, we found significant differences in TEG FF MA and ROTEM MCF between placebo- and fibrinogen-treated groups over hospitalization time. ROTEM FIBTEM MCF seemed to be more consistent with the duration of the between-group difference, as indicated by fibrinogen levels, than TEG FF MA. There were significant correlations between corresponding parameters of TEG FF and ROTEM FIBTEM, with TEG FF MA and ROTEM FIBTEM MCF showing the strongest correlation ( $\rho = 0.80$ ,  $p < 0.001$ ); however, they were not interchangeable, and MA was larger than MCF. In addition, ROTEM CT and LI30 indicated the effect of fibrinogen administration on coagulation time and fibrinolysis. There were discrepancies between TEG and ROTEM in their detection of coagulation abnormalities, hypofibrinogenemia, and hyperfibrinolysis (Peng et al. 2018).

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## New Viscoelastic Hemostatic Testing Systems

New and fully automated (no pipetting) TEG and ROTEM systems (TEG 6 s [Haemonetics Corp.] and ROTEM sigma [Instrumentation Laboratory]) are now available. Both work with four-channel cartridges but are based on different mechanisms. TEG 6 s uses a new technology termed “coagulation resonance analysis” and microfluidic cartridges containing dried reagents (Gurbel et al. 2016). ROTEM sigma operates on the same pin and cup technology as ROTEM delta but uses cartridges containing lyophilized bead reagents instead of liquid reagents (Görlinger et al. 2016).

TEG 6 s reportedly is highly reliable, with results strongly correlating with those derived from TEG 5000 (linear correlation estimates  $>0.9$ ) (Neal et al. 2020). ROTEM sigma also has a high precision, with results being strongly correlated with those derived from ROTEM delta (Pearson correlation coefficients  $\geq 0.8$ ) (Schenk et al. 2019). Furthermore, when compared for use in trauma patients, strong to very strong correlations (Spearman correlation coefficients  $>0.6$ ) were observed between corresponding TEG 6 s and ROTEM sigma parameters, although there were significant differences in absolute values for most measurements (Ziegler et al. 2019).

Furthermore, other viscoelastic hemostatic testing systems are available and emerging (Hartmann et al. 2020b). Sonoclot is a legacy device developed by Sienco, Inc. The Sonoclot device differs from TEG and ROTEM in that it is not a rotational-based system but a linear motion system (Ganter and Hofer 2008). Quantra hemostasis analyzer is a relatively new product developed by HemoSonics based on a proprietary technology that uses ultrasound to measure clot time and clot stiffness from changes in viscoelastic properties of whole blood during coagulation (Ferrante et al. 2016). Multicenter evaluation of the Quantra system in adult patients undergoing major surgical procedures consisting primarily of cardiac and major orthopedic surgeries was conducted, showing that the correlation between ROTEM and Quantra was very strong with correlation coefficients ranging between 0.84 and 0.89. (Groves et al. 2020). Additional receiver operating characteristics analysis indicated sensitivities and specificities in the 80–90% range when Quantra parameters were used to discriminate ROTEM threshold values currently used in goal-directed treatment algorithms. Several emerging technologies are currently in development for point-of-care viscoelastic hemostatic testing, including microfluidics, fluorescent microscopy, electrochemical sensing, photoacoustic detection, and micro-/nano-electromechanical systems (MEMS/NEMS) (Mohammadi Aria et al. 2019).

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## Applications to Diagnosis of TIC and Hypofibrinogenemia

Historically, TIC is defined by CCTs, such as INR above a threshold of 1.2 (Frith et al. 2010; Meyer et al. 2014; Davenport et al. 2011; Hagemo et al. 2015), 1.3 (Tonglet et al. 2018; Kornblith et al. 2014; Cohen et al. 2013), 1.5 (Niles et al. 2008), and 1.6 (Rugeri et al. 2007), PTT  $\geq 35$  s (Cohen et al. 2013); by plasma fibrinogen levels, ranging from 1.0 to 2.0 g/L; and by platelet counts below  $100 \times 10^9/L$  (Rossaint et al. 2016). However, this is no sound evidence to support the usefulness of these tests in particular INR, PTT for diagnosis of coagulopathy, or to guide hemostatic therapy (Haas et al. 2015). There are several limiting factors with these assays, such as the time to obtaining results from multiple tests; sole measurement of contribution of plasma proteins to clot formation, without regard for the central role of platelets; and the inability to identify hyperfibrinolysis (Moore et al. 2021). The use of CCTs such as INR in trauma has been severely criticized due to the lack of association with bleeding and blood transfusion. It has been reported that INR

overestimated coagulopathy and should not be used to guide blood transfusion in stable trauma and surgical patients (McCully et al. 2013).

Consequently, viscoelastic hemostatic tests in particular TEG and ROTEM have been adopted for the diagnosis of TIC, owing to their assessment of whole blood clot formation and degradation in real time, and rapid availability of the comprehensive information. TEG has been shown to identify additional coagulopathies compared to CCT methods (Sumislawski et al. 2019). TEG and ROTEM can detect different fibrinolysis phenotypes in trauma (Stettler et al. 2019).

Table 2 summarizes the literature on the use of viscoelastic hemostatic tests for diagnosis of TIC according to test done (TEG or ROTEM) and the study design, method of blood sampling, activators used, and parameters studied along with main findings.

TIC was defined by celite- and kaolin-activated TEG, respectively, when  $\geq 2$  TEG parameters are abnormal (Kaufmann et al. 1997; Rizoli et al. 2011). TIC was also defined according to rapid TEG if any of the following variables were abnormal (Holcomb et al. 2012; Ostrowski et al. 2017): ACT > 128 s, R time > 66 s, K > 150 s, Alpha < 56°, MA < 55 mm, and LY30 > 3%. When defined by kaolin TEG, one or several of the TEG parameters could be abnormal to indicate coagulopathy in an algorithm with R  $\geq 11$  min, MA  $\leq 50$  mm, angle < 52°, or LY30 > 8% (Johansson et al. 2010). Rapid TEG is faster than kaolin TEG and CCTs for providing reliable information on coagulopathy in patients with multiple injuries (Jeger et al. 2009).

TEG and ROTEM could detect a hypercoagulable state, hyperfibrinolysis, and were better tests than PT or PTT (Branco et al. 2014; Park et al. 2009; Schreiber et al. 2005; Spasiano et al. 2022; Watters et al. 2010). However, single TEG R performed worse than INR at identifying vitamin K-dependent coagulation factor deficiency (Nascimento et al. 2012).

TIC was defined by hypocoagulable state on ROTEM which was determined by one of the principle parameters (CT, CFT, MCF, ML) outside the manufacturer's normal ranges by 20% (i.e., CT  $\geq 94$  s, CFT  $\geq 190$  s, MCF  $\leq 40$  mm, ML  $\geq 12\%$ ) (Tonglet et al. 2018). EXTEM which includes the platelet contribution to the development of coagulation abnormalities would be more suitable to detect coagulopathy. EXTEM CA5  $\leq 35$  mm could predict massive transfusion and was used to define TIC (Rourke et al. 2012). EXTEM CA5  $\leq 35$  mm (Davenport et al. 2011) and  $\leq 37$  mm (Hagemo et al. 2015) threshold values for detection of TIC resulted in a detection rate of 77% and 66.3%, respectively, and FIBTEM CA5  $\leq 8$  mm detected TIC in 67.5%, while fibrinogen concentration  $\leq 1.6$  g/L detected TIC in 73.6% (Hagemo et al. 2015). TIC defined by EXTEM MCF < 40 mm was 39% in combat casualties (Woolley et al. 2013). ROTEM also detected more abnormal coagulation status than CCTs (PT and PTT) in a deployed military setting (Doran et al. 2010) as well as in-hospital emergency department (Spagnolello et al. 2021). EXTEM MCF showed 100% sensitivity and specificity for detection of hyperfibrinolysis defined as a euglobulin lysis time (ELT) < 90 min (Levrat et al. 2008). Combined with INR > 1.2, EXTEM A5  $\leq 35$  mm and/or LI30 < 97% on admission classified 15% more patients with TIC and predicted massive transfusion

**Table 2** Viscoelastic hemostatic tests (TEG and ROTEM) for diagnosis of TIC

Study type	Tests and blood samples	Parameters and cutoff values	Definition of TIC/abnormal coagulation	Main findings	References
Prospective observational cohort study of 69 adult blunt trauma patients with a median ISS of 5 (range, 1–75)	Celite-activated TEG (model 3000) native blood	R 5–7 min K 1.5–3 min $\alpha$ angle 54–67° MA	PT/PTTs normal, 11.0–14.0 and 25–36	Forty five patients were hypercoagulable (mean ISS 13.1), and 7 were hypocoagulable (mean ISS 28.6). TEG is predictive of early blood transfusion with the first 24 h of admission	Kaufmann et al. (1997)
Prospective observational study of 65 patients with mean injury severity score was $23 \pm 12$	Kaolin TEG with native blood	R, $\alpha$ , MA	R < 3.7 min for hypercoagulability	Significant correlation only on day 1; between R and PTT, MA and platelets hypercoagulability in the first 24; women more hypercoagulable	Schreiber et al. (2005)
Prospective observational study of 20 patients with a median ISS of 29 (range 16–65)	Kaolin and rapid TEG with native blood	R, K, $\alpha$ , MA rapid TEG: >2 min, $\alpha$ < 66°, MA < 54 mm; for kaolin TEG: R > 8 min, K > 4 min, $\alpha$ < 47°, MA < 54 mm	INR > 1.25, aPTT > 36 s, thrombin time > 15 s, platelet count < 150 nL	Strong correlation between k, $\alpha$ , and MA in rapid TEG and TEG; moderate correlation between k/ $\alpha$ /MA and platelet count and INR, no significant correlations were found between TEG parameters and TT or aPTT. Rapid TEG provides a fast and reliable indication of coagulation status in trauma patients	Jeger et al. (2009)

(continued)

Table 2 (continued)

Study type	Tests and blood samples	Parameters and cutoff values	Definition of TIC/abnormal coagulation	Main findings	References
Prospective observational study of nonburn trauma patients ( $n = 33$ ) with an average ISS of 21.7, burned patients ( $n = 25$ ) with an average of ISS of 18.1	Rapid TEG with native blood	R, $\alpha$ , MA, LY30	Healthy volunteers ( $n = 20$ )	$\alpha$ and MA were greater in patients than in controls; TEG was more sensitive than PT and PTT, to hypercoagulable state in post-injury, non-bleeding patients	Park et al. (2009)
Prospective observational study of 30 trauma patients with splenectomy	Kaolin TEG	R, K, $\alpha$ , MA, LY30	Splenic preservation group ( $n = 50$ )	MA significantly greater postsplenectomy; platelet and fibrinogen remained higher; persistent hypercoagulable state after splenectomy	Watters et al. (2010)
Prospective observational cohort study of 110 severely traumatized patients with an ISS $\geq 16$	Kaolin TEG with citrated blood	R, K, $\alpha$ , MA $\geq 2$ abnormal parameter values	Clotting factor (II, V, VII, VIII, IX, X, XI, and XII deficiency ( $\geq 30\%$ activity)	TEG had a sensitivity of 35.3% (14.2%, 61.7%), specificity of 88.8% (79.7%, 94.7%), PPV of 40.0% (16.3%, 67.7%), and NPV of 86.6% (77.3%, 93.1%) for critical clotting factor deficits	Rizoli et al. (2011)
Prospective observational cohort study of 219 patients with an ISS $26 \pm 12$	Kaolin TEG with citrated blood	R > 8 min	Vitamin K-dependent coagulation factor (II, VI, IX, and X) deficiency ( $\geq 50\%$ activity)	TEG had a sensitivity of 33% (95% CI, 16%–55%), specificity of 95% (95% CI, 91%–98%), PPV of 47% (95% CI, 23%–72%), and NPV of 92% (95% CI, 87%–95%) in detecting coagulation factor deficiency	Nascimento et al. (2012)

<p>a single-center, retrospective cohort study of 1974 trauma patients with a median ISS of 17 (9, 26)</p>	<p>Rapid TEG with citrated blood</p>	<p>ACT 86–118 s R 0–1 min K 1–2 min <math>\alpha</math> angle 66–82° MA 54–72 mm LY30 0.0–7.5%</p>	<p>PT, aPTT, INR, platelet count, and fibrinogen concentration</p>	<p>Rapid TEG was clinically superior to CCTs for identifying patients with an increased risk of early RBC, plasma and platelet transfusions, and fibrinolysis</p>	<p>Holcomb et al. (2012)</p>
<p>Prospective observational study of 404 trauma patients with a median ISS of 17 (9–26)</p>	<p>Rapid TEG with citrated blood</p>	<p>ACT &gt; 128 s, R &gt; 1.1 min, K &gt; 2.5 min, <math>\alpha</math> &lt; 56°, MA &lt; 55 mm, and LY30 &gt; 3%</p>	<p>TG lag time <math>\geq</math> 4.9 min, ETP &lt; 1000 nM*min, peak &lt; 250 nM, time to peak <math>\geq</math> 7 min, rate of TG <math>\leq</math> 100 nM/min</p>	<p>One third (35%) of the patients had rapid TEG coagulopathy which was associated with sympathoadrenal activation, endotheliopathy, and increased mortality</p>	<p>Ostrowski et al. (2017)</p>
<p>Prospective observational study of 45 trauma patients with a median ISS of 24.0 (17.5–29.0)</p>	<p>TEG FF with citrated blood</p>	<p>MA 1–24 mm</p>	<p>INR <math>\geq</math> 1.2 fibrinogen concentration &lt; 1 g/L</p>	<p>TEG FF MA poorly detected coagulopathy as defined by INR <math>\geq</math> 1.2 (AUC 0.557 (0.480–0.634) but well predicted hypofibrinogenemia (fibrinogen concentration &lt; 1 g/L) (AUC 0.948 (0.886–1.000))</p>	<p>Peng et al. (2019)</p>
<p>Prospective observational 2 years cohort study on 83 severe trauma patients with a mean new ISS of 36 (<math>\pm</math>13)</p>	<p>Kaolin TEG</p>	<p>R 9–27 min MA 44–64 mm G 3.6–8.5 dyne/s <math>\geq</math> 2 abnormal parameter values LY30 &gt; 3%</p>	<p>INR &gt; 1.5 LY30 &gt; 3% hyperfibrinolysis</p>	<p>88.8% of the trauma population had coagulation abnormalities immediately after the trauma; with 71.3% procoagulant changes and 8.8% hyperfibrinolysis</p>	<p>Spasiano et al. (2022)</p>

(continued)

**Table 2** (continued)

Study type	Tests and blood samples	Parameters and cutoff values	Definition of TIC/abnormal coagulation	Main findings	References
ROTEM					
Prospective observational study of 88 patients with an ISS of 22 (12–34)	EXTEM, INTEM, FIBTEM	EXTEM CA15 < 32 mm  INTEM CFT 112 s  INTEM CA15 < 46 mm  FIBTEM CA10 < 5 mm	PT > 1.5 of control value  APTT > 1.5 of control value  Platelet count < $50 \times 10^9/L$  Fibrinogen < 1 g/L	EXTEM CA15 had a sensitivity of 87 (72–87), specificity of 100 (99–100), PPV of 100 (83–100), NPV of 99 (98–99), AUC of 0.98 in predicting PT > 1.5 of control value  INTEM CFT has a sensitivity of 100 (84–100), specificity of 74 (73–74), PPV of 23 (19–23), NPV of 100 (98–100), and AUC of 0.94  INTEM CA15 has a sensitivity of 100 (71–100), specificity of 83 (82–83), PPV of 17 (12–17), NPV of 100 (98–100), and AUC of 0.92  FIBTEM CA10 had a sensitivity of 91 (72–93), specificity of 85 (84–86), PPV of 55 (45–60), NPV of 99 (97–100), and AUC of 0.96	Rugeri et al. (2007)



Prospective observational study of 23 patients with a median ISS of 38 (24–75)	INTEM and EXTEM	CT, CFT, MCF, EXTEM CA10 ≤ 10 mm, CA15 ≤ 12 mm, MCF ≤ 18 mm; LI30 ≤ 71%, LI60 ≤ 1%; FIBTEM; APTEM	Hyperfibrinolysis was defined as a ELT < 90 min	EXTEM MCF correlated better with ELT ( $r^2 = 0.68$ ) than LI60 ( $r^2 = 0.63$ ), CA10 ( $r^2 = 0.53$ ) or LI30 ( $r^2 = 0.15$ ). ROTEM accurately and rapidly diagnosed hyperfibrinolysis. At the threshold of 18 mm (EXTEM MCF), 71% (LI30) and 7% (increase of APTEM MCF), the sensitivity for detection of hyperfibrinolysis was 100%, 75%, and 80%, respectively, with a specificity of 100%	Levrat et al. (2008)
Prospective observational field study of 25 combat trauma patients	EXTEM INTEM FIBTEM	CT, CFT, MCF, ML < 15%	PT > 18 s, and PTT > 60 s	Standard laboratory testing showed that 10% of all patients were coagulopathic on admission compared with 64% with an abnormal ROTEM trace ( $p = 0.0005$ )	Doran et al. (2010)
Prospective observational study of 300 patients with ISS of 12 (4–25)	EXTEM with citrated blood	CT > 94 s, $\alpha < 65^\circ$ , CA5 ≤ 35 mm	PT ratio > 1.2	CFT, $\alpha$ , CA5, MCF significantly different in group with coagulopathy; CA5 predicts transfusion better than PT and rapidly diagnoses coagulopathy and predicts transfusion	Davenport et al. (2011)

(continued)

Table 2 (continued)

Study type	Tests and blood samples	Parameters and cutoff values	Definition of TIC/abnormal coagulation	Main findings	References
48 severe trauma patients including 31 battlefield casualties with ISS of 34	EXTEM with citrated blood	CA5 < 32 mm and CA10 < 40 mm	MCF < 40 mm	CA5 and CA10 predicted hypocoagulation in individual samples with sensitivities/specificities [95% CI] of 0.96 [0.91–1.00]/0.58 [0.45–0.71] (CA5) and 1.00/0.70 [0.58–0.82] (CA10), respectively	Woolley et al. (2013)
Observational cohort study of 808 patients with an median ISS of 16	EXTEM and FIBTEM	EXTEM CA5 ≤ 37 mm and FIBTEM CA5 ≤ 8 mm	INR > 1.2	Sensitivity for diagnosis of TIC is 66.3% (55.1–76.3) and 67.5% (55.9–77.8), respectively; specificity 81.2% (15.9–21.9) and 100–79.3 (17.7–23.9); PPV 29.9 (23.4–37.1) and 26.9 (20.8–33.8); NPV 95.2 (93.2–96.8) and 95.6 (93.5–97.1); AUC 0.79 (0.76–0.81) and 0.80 (0.77–0.83)	Hagemo et al. (2015)
Prospective observational study of 45 trauma patients with a median ISS of 24.0 (17.5–29.0)	EXTEM and FIBTEM	MCF 52–70 mm and 7–24 mm	INR ≥ 1.2 fibrinogen concentration < 1 g/L	EXTEM and FIBTEM MCF poorly detected coagulopathy as defined by INR ≥ 1.2 (AUC 0.564 (0.488–0.640); 0.609 (0.535–0.683), but well predicted hypofibrinogenemia	Peng et al. (2019)

Prospective observational study of 40 trauma patients with a median ISS of 22 (CI 14–27)	EXTEM citrated blood	EXTEM CA5 ≤ 35 mm EXTEM LI30 < 97%	INR > 1.2	(fibrinogen concentration < 1 g/L) (AUC 0.920 (0.833–1.000); 0.962 (0.900–1.000))	Cohen et al. (2019)
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Fibrinogen concentration

Observational cohort study of 808 patients with an median ISS of 16	Clauss method	≤1.61 g/L	INR > 1.2	Fibrinogen concentration had a sensitivity of 73.6 (63.0–82.4), specificity of 100–11.5 (9.2–14.1), PPV of 45.1 (36.7–53.6), NPV of 96.3 (94.5–97.7), and AUC 0.87 (0.84–0.89) in detecting TIC	Hagemo et al. (2015)
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Data represent medians and interquartile range, unless specified. *ACT* activated clotting time, *aPTT* activated partial thromboplastin time, *AUC* area under the curve, *CI* confidence interval, *ELT* euglobulin lysis time, *ETP* endogenous thrombin potential, *GCS* Glasgow coma scale, *INR* international normalized ratio, *ISS* injury severity score, *NPV* negative predictive value, *NR* not reported, *PPV* positive predictive value, *PT* prothrombin time, *TBI* traumatic brain injury, *TG* thrombin generation

with higher sensitivity (86% vs. 64%) than  $\text{INR} > 1.2$  alone in military trauma patients (Cohen et al. 2019).

High-quality studies are need for diagnosis of TIC using viscoelastic devices (Sakamoto et al. 2017). Additionally, a clinical scoring system for assessing TIC, which includes subclassifications for the anatomic location of injury and interventions required for bleeding control, has been proposed (Neal et al. 2015). European trauma experts recommend a grading system comprising three severity levels based on fibrinogen level, INR, and platelet count, to define TIC (Černý et al. 2022).

Table 3 summarizes the predictive accuracy of TEG FF and ROTEM FIBTEM for hypofibrinogenemia in trauma. MA and MCF are the main parameters used for the predictions of hypofibrinogenemia and blood transfusions. The prediction accuracy was evaluated by sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) and variate regression analyses. Different cutoff values of fibrinogen concentrations ranging from 1 to 1.8 g/L were used to define hypofibrinogenemia. Traditionally, a plasma fibrinogen level of 1 g/L was established for fibrinogen replacement in patients with congenital fibrinogen deficiency, whereas the threshold varied from 0.8 to 2.0 g/L in patients with acquired fibrinogen deficiency (Levy et al. 2014). In contrast, a critical fibrinogen concentration of 2.29 g/L was identified in trauma below which a significant increase in mortality occurred (Hagemo et al. 2014). The discrepancy implies that the negative impact of fibrinogen deficiency in trauma may have been underestimated. It should also be noted that hypofibrinogenemia prevalence in major bleeding varies across clinical contexts (McQuilten et al. 2017b).

Most clinical studies of hypofibrinogenemia in trauma are prospective observational, while a few are retrospective and randomized controlled. Sample size ranged from 23 to 1077 patients. In contrast with ROTEM, TEG FF has been used less to detect hypofibrinogenemia and predict blood transfusion requirements. Among various clinical settings, ROTEM FIBTEM has been mostly used in trauma, cardiac surgery, and liver transplantation with best predictive power for hypofibrinogenemia (fibrinogen  $< 1.5$  g/L) (AUC = 0.99) in cardiac surgery (Bhardwaj et al. 2017). Furthermore, several studies have shown that TEG FF and ROTEM FIBTEM could predict bleeding and transfusion requirements in trauma (Johansson et al. 2013; Schöchel et al. 2011), with various accuracies. It appeared that ROTEM would have better predictive accuracy than TEG because it has greater specificity for some common coagulopathies in cardiac surgery, such as fibrinogen deficiency. The averaged likelihood ratio of TEG FF MA for diagnosis of hypofibrinogenemia is  $4.71 \pm 2.18$  based on a number of studies (Gautam et al. 2017; Meyer et al. 2015; Peng et al. 2018), while the corresponding value of ROTEM FIBTEM MCF is  $9.24 \pm 2.64$  calculated from the literature (Meyer et al. 2015; Peng et al. 2018; Jeong et al. 2015).

Only a few studies demonstrated ROTEM FIBTEM provided faster and better prediction than plasma fibrinogen concentration for massive transfusion (Schöchel et al. 2011) and bleeding (Dötsch et al. 2017), respectively. ROTEM FIBTEM provided early prediction of massive transfusion in trauma similar to the most predictive laboratory parameters (e.g., fibrinogen and hemoglobin concentrations)

**Table 3** Clinical evaluation of TEG and ROTEM functional fibrinogen tests for diagnosis of hypofibrinogenemia in trauma

Study design and patients	Blood collection and analysis	Findings	Ref.
<b>TEG FF</b>			
Randomized controlled trial of trauma patients at risk of significant hemorrhage ( $n = 45$ , ISS = 18–29) receiving either 6 g fibrinogen concentrate (RiaSTAP™) or placebo (normal saline)	Citratd whole blood was collected from the randomized trauma patients at admission, 1-, 3-, 11-, 23-, and 47-h post-infusion time. Standard FF TEG was performed on a computerized TEG Hemostasis System 5000 (Haemonetics Corporation, Haemoscope Division, Niles, IL, USA) according to the manufacturer's protocol	FF TEG MA predicted hypofibrinogenemia (fibrinogen concentration < 1 g/L) and 24-h plasma transfusion with high accuracies (AUC = 0.95, $p = 0.002$ and AUC = 0.70, $p = 0.042$ )	Peng et al. (2018)
A prospective study of 182 adult trauma patients with a median ISS of 17 (9–26)	Blood was sampled immediately upon arrival to trauma center and evaluated in tissue factor-activated and platelet-inhibited TEG (i.e., FF TEG) precisely 1 h after sampling by a hemostasis analyzer system (TEG 5000, Haemonetics Corp., Braintree, MA) according to the manufacturer's recommendations. All analyses were conducted at 37 °C	Sensitivity, specificity and AUC of TEG FF MA for detection of fibrinogen <1.5 g/L were 77%, 81% and 0.869, respectively. TEG FF MA was also a univariate predictors of massive transfusion (>10 units of RBCs) at 6 and 24 h with odd ratios of 0.79 and 0.82 and mortality at 28 days with a hazard ratio of 0.84	Johansson et al. (2013), Meyer et al. (2015)
<b>ROTEM FIBTEM</b>			
Randomized controlled trial of trauma patients at risk of significant hemorrhage ( $n = 45$ , ISS = 18–29) receiving either 6 g FC (RiaSTAP™) or placebo (normal saline)	Citratd whole blood was collected from the trauma patients at admission, 1-, 3-, 11-, 23-, and 47-h post-infusion time. Standard ROTEM FIBTEM was performed on a ROTEM delta system (tem innovations GmbH, Munich, Germany; succeeded by instrumentation	ROTEM FIBTEM MCF predicted hypofibrinogenemia (fibrinogen concentration < 1 g/L) and 24-h plasma transfusion with high accuracies (AUC = 0.96, $p < 0.001$ ) and AUC = 0.72, $p = 0.023$ )	Peng et al. (2018)

(continued)

**Table 3** (continued)

Study design and patients	Blood collection and analysis	Findings	Ref.
	laboratory, Bedford, MA, USA) according to the manufacturer's protocol		
A prospective observational study of 88 trauma patients an median ISS score of 22 (12–34)	Blood samples were collected immediately after the patient's arrival to the trauma room (H0) and at 6 h (H6), 12 h (H12), and 24 h (H24) after admission, representing a total of 270 samples. The ROTEM measurements and standard coagulation tests were performed within 2 h of collection of blood samples	Sensitivity, specificity and AUC of FIBTEM A10 for detection of fibrinogen <1 g/L were 91%, 85% and 0.96, respectively	Rugeri et al. (2007)
A retrospective analysis of data from 323 patients with an injury severity score (ISS) $\geq 16$ (20–50)	Blood samples were taken immediately upon admission to ER. ROTEM analyses (EXTEM, INTEM, FIBTEM) were typically performed at the bedside within minutes of sample collection. Fibrinogen concentration was measured by the Clauss method (STA-fib assay (Roche diagnostics GmbH); optical read-out), using a STA compact machine (Roche diagnostics GmbH, Vienna, Austria)	Sensitivity, specificity and AUC of FIBTEM A10/MCF for prediction of massive transfusion ( $\geq 10$ units RBC transfused in 24 h) 63.3/77.5%, 83.2/74.9%, 0.83/0.84 (95% CI 0.78–0.87/0.79–0.88), similar to fibrinogen concentration	Schöchli et al. (2011)
A prospective cohort study of 517 trauma patients with a median ISS of 14 (8–27)	Blood was drawn from either the femoral vein or antecubital fossa into a 2.7-mL citrated vacutainer within 20 min of arrival in the emergency department (ED). ROTEM tests were performed within 2 h of blood draw with a ROTEM delta instrument, at 37 °C	Sensitivity, specificity and AUC of FIBTEM A5 for detection of fibrinogen <1.5 g/L 87%, 70% and 0.8 (95% CI 0.7–0.9)	Rourke et al. (2012)

(continued)

**Table 3** (continued)

Study design and patients	Blood collection and analysis	Findings	Ref.
A prospective, single-center, noninterventional, noncontrolled, open clinical study of 50 trauma patients with a median ISS of 13 (4–66)	Blood was collected at hospital admission, 3- and 24-h after admission and analyzed by ROTEM assays (EXTEM and FIBTEM). EXTEM was considered positive if one of the four principle parameters (CT, CFT, MCF, and maximum lysis) greater than 20% of the expected highest or lowest normal value of the manufacturer normal value ranges (CT $\geq$ 94, CFT $\geq$ 190, MCF $\leq$ 40, ML $\leq$ 12). FIBTEM was considered positive if MCF was at least 20% smaller than the expected mean normal value (MCF $\leq$ 7)	Sensitivity, specificity, and AUC of FIBTEM MCF $<$ 7 mm within normal EXTEM patients are 100%, 90.2%, and 0.951 and 0%, 87.5%, and 0.563 for predictions of coagulopathy (INR $\geq$ 1.3) and mortality at 30 days	Tonglet et al. (2018)
A prospective study of 182 adult trauma patients with a median ISS of 17 (9–26)	Blood was sampled immediately on hospital arrival. FIBTEM assays were performed with citrated blood precisely 1 h after sampling according to the manufacturer's recommendations. Fibrinogen level was determined by Clauss method	Sensitivity, specificity and AUC of FIBTEM MCF $<$ 10 mm were 80%, 89%, and 0.889 for detection of fibrinogen $<$ 1.5 g/L	Meyer et al. (2015)

*AUC* area under the receiver operating characteristic curve, *CI* confidence interval, *CPB* cardiopulmonary bypass, *ICU* intensive care unit, *ISS* injury severity score

(Schöchrl et al. 2011). A separate study comparing standard fibrinogen measurement methods (i.e., Clauss method and thrombin clotting time) with ROTEM FIBTEM in patients with cirrhosis suggested FIBTEM as a promising alternative to standard plasma fibrinogen measurement in cirrhotic patients, especially in evaluating fibrin polymerization disorders in these patients (Vucelic et al. 2015).

There is insufficient evidence or low-quality evidence for the benefits of TEG and ROTEM for the prediction of bleeding and adverse outcomes beyond that achieved using routinely measured baseline factors or CCTs except for rapidity. ROTEM EXTEM and FIBTEM were no better than routine laboratory tests for detecting

differences between surviving and nonsurviving critically ill patients (Larsson et al. 2015). ROTEM FIBTEM was not a good test to predict the presence of acute coagulopathy of trauma defined as an INR  $> 1.3$  or a fibrinogen level  $< 1.5$  g/L unless combined with EXTEM, and either of the tests could predict the need for emergent blood product transfusions (defined as  $\geq 5$  units of RBC and  $\geq 3$  units of plasma within the first 24 h of care) (Tonglet et al. 2018).

Finally, if fibrinogen deficiency has a causal relationship with bleeding and adverse clinical outcomes, it is sensible to suggest that TEG and ROTEM FF tests that improve clinical prediction for fibrinogen-related bleeding may also have the potential to predict adverse clinical outcomes. However, randomized trials are needed to provide high-quality evidence for the role of TEG and ROTEM in diagnosis, management, and monitoring of fibrinogen function and replacement in bleeding patients.

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## Assessment of the FF Level and Hemostatic Effect of Fibrinogen Replacement

The Clauss test is considered a standard FF test for determining the plasma fibrinogen level, although other methods, such as the prothrombin time-derived method (Blasi et al. 2012) and enzyme-linked immunosorbent assay (ELISA) (Kalina et al. 2008), are also used. However, ELISA does not discriminate between functional and nonfunctional immunoreactive fibrinogen proteins or even some fibrinogen degradation products (Mackie et al. 2002).

The Clauss method is limited to low levels of heparin (which inactivate thrombin through antithrombin III), which is a serious limitation to its use in cardiac surgery. It may be affected by fibrin degradation products and polymerization inhibitors as well as inhibitors of fibrin formation (Koh et al. 1994). Its turnaround time is approximately 40 min (Asmis 2015). In comparison, the TEG and ROTEM FF tests can be completed in 15 min and provide rapid and accurate detection of hyperfibrinolysis (Schöchel et al. 2010a). Another advantage of TEG and ROTEM is that they can be used for fully heparinized patients (Solomon et al. 2012; Gertler et al. 2011).

TEG has been used to study *in vitro* effects of fibrinogen on coagulation of plasma deficient in coagulation factors and diluted by colloids (Nielsen et al. 2005; Nielsen 2005). It has been used to monitor the effect of a cardiopulmonary bypass system with biocompatible coating on fibrinogen levels (Fluger et al. 2011). ROTEM has been used to determine the usefulness of fibrinogen substitution to reverse dilutional coagulopathy in *in vitro* (Fries et al. 2006), animal (Fries et al. 2005), and *ex vivo* models (Fenger-Eriksen et al. 2005). *In vitro* study showed dose-dependent increase in ROTEM MCF with the amount (0–3 mg/mL) of FC (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) added to normal human plasma pool, fibrinogen-deficient plasma pool, and individual plasma samples from 17 patients with fibrinogen deficiency (Kalina et al. 2008). All these studies showed that to various extents, fibrinogen improved clot strength (MA or MCF), clot formation (R or CT), and clot propagation ( $\alpha$ ) as measured by TEG or ROTEM.



In addition, ex vivo ROTEM studies indicated that administration of 6 g FC to samples of coagulopathic trauma patients could correct FIBTEM CA5 and MCF to the level of patients with minor injury (Rourke et al. 2012). In contrast, the ex vivo addition of cryoprecipitate at a standard dose of cryoprecipitate (equivalent to 2.6 g fibrinogen) was unable to reverse the coagulopathy until a high dose (equivalent to 7.8 g).

As summarized in Table 4, a number of clinical studies on TEG and ROTEM tests, especially those on ROTEM FIBTEM, have assessed hemostatic effects of FC administration in major trauma (Peng et al. 2019; Rourke et al. 2012; Ponschab et al. 2015; Schlimp et al. 2013a; Innerhofer et al. 2013, 2017; Schöchler et al. 2010b; Ziegler et al. 2021), including early cryoprecipitate transfusion (Curry et al. 2015), cardiovascular surgery with cardiopulmonary bypass (Schlomp and Schöchler 2014; Gautam et al. 2017; Meyer et al. 2015), liver transplantation (Görlinger et al. 2013; Peng et al. 2018), and orthopedic surgery (Jeong et al. 2015). Unless specified otherwise, the TEG and ROTEM tests were performed using TEG 5000 and ROTEM delta and the reagents and procedures recommended by the respective manufacturers.

Most of these clinical studies were randomized and controlled (Peng et al. 2019; Innerhofer et al. 2017; Curry et al. 2015; Ziegler et al. 2021; Nascimento et al. 2016), whereas a few were prospective, observational, or retrospective (Ponschab et al. 2015; Schlomp et al. 2013a; Innerhofer et al. 2013; Schöchler et al. 2010b; Seebold et al. 2019). Fibrinogen replacement was conducted preemptively or was guided by ROTEM or TEG. ROTEM FIBTEM has been well used in trauma, showing a dose-dependent increase in MCF immediately after fibrinogen administration. The hemostatic effect could last from 4 to 48 h (Peng et al. 2019; Wikkelsø et al. 2015). Furthermore, several studies have shown that the TEG FF- and ROTEM FIBTEM-measured hemostatic effect mirrored plasma fibrinogen profiles in response to fibrinogen replacement (Peng et al. 2019; Curry et al. 2015).

Some of these studies also used ROTEM to guide FC administration (Ponschab et al. 2015; Schlomp et al. 2013a; Innerhofer et al. 2013, 2017; Schöchler et al. 2010b). Few studies on the effects of FC administration on TEG FF have been reported (Peng et al. 2019), although some have shown a correlation between TEG FF MA and the Clauss fibrinogen level (Kornblith et al. 2014; Harr et al. 2013). Alternatively, TEG FF has been used to measure the effect of fibrinogen levels on heparin resistance/thromboprophylactic treatment in trauma (Harr et al. 2014).

Fibrinogen is not the only contributor to TEG FF and ROTEM FIBTEM CAs, which may limit their utility for the assessment of the hemostatic effect of fibrinogen replacement. Activated factor XIII and hematocrit levels may affect clot firmness as well (Schlomp et al. 2013b; Solomon et al. 2013b; Nielsen et al. 2004; Ogawa et al. 2012; Thomas et al. 2016). In one study, postoperative factor XIII levels correlated with FIBTEM MCF more significantly than fibrinogen levels in patients undergoing major upper gastrointestinal surgery (Thomas et al. 2016). The same study showed a significant correlation between platelet count and ROTEM FIBTEM MCF ( $r = 0.55$ ,

**Table 4** Hemostatic effects of fibrinogen replacement as measured by TEG and ROTEM

Clinical setting	Study design	Fibrinogen replacement and TEG/ROTEM test	Results	References
Preemptive fibrinogen replacement				
Trauma	Single-center, randomized, controlled, double-blind feasibility trial of adult trauma patients requiring blood transfusion and randomly and preemptively treated with FC ( $n = 21$ ) or normal saline (placebo, $n = 24$ )	Within 1 h after hospital admission, 95% of patients received a single dose of 6 g FC (RiaSTAP, CSL Behring GmbH, King of Prussia, PA, USA). ROTEM FIBTEM and TEG FF were performed at hospital admission and 2, 4, 12, 24, and 48 h after admission	TEG FF MA and ROTEM FIBTEM MCF mirrored plasma fibrinogen profiles and reached a maximum difference between the two groups at 1–3 h after fibrinogen administration. TEG FF MA for placebo patients was significantly lower than that for FC patients at all time points ( $p \leq 0.019$ ) during the 48-hr hospitalization, except at admission ( $p = 0.11$ ). ROTEM FIBTEM CT and MCF showed between-group differences 2–24 h after admission ( $p \leq 0.028$ for CT and $P \leq 0.002$ for MCF)	Nascimento et al. (2016), Peng et al. (2019)
	Randomized, placebo-controlled, double-blind trial of adult trauma patients treated with FC ( $n = 28$ ) or placebo (25) before hospital admission	FC (Clottafact, LFB, Les Ulis, France) at a dosage of 50 mg/kg body weight or an equivalent amount of placebo was administered on site or during transportation to the study center. ROTEM FIBTEM at baseline (onsite, prior to study drug administration) and on ED admission and 3, 9, 24, and 48 h and 7 days after ED admission	Median FIBTEM MCF decreased in the placebo group between the baseline and ED admission, from 12.5 (interquartile range: 10.5–14) mm to 11 (9.5–13) mm, $P = 0.0226$ but increased in the FC group from 13 (11–15) mm to 15 (13.5–17) mm, $P = 0.0062$ . The median between-group difference in FIBTEM MCF was 5 (3–7) mm, $P < 0.0001$	Ziegler et al. (2021)

(continued)

**Table 4** (continued)

Clinical setting	Study design	Fibrinogen replacement and TEG/ROTEM test	Results	References
	Randomized, controlled trial of adult trauma patients with ISS $\geq 15$ who received 10 U of cryoprecipitate and MHT or MHT alone	Eighty-five percent of patients received cryoprecipitate (CRYO) within 90 min after hospital admission. Blood samples were drawn for ROTEM tests immediately upon admission, during active bleeding (immediately after transfusion of 4, 8, and 12 U RBC), and 24 and 72 h after randomization	FIBTEM data mirrored changes in Clauss fibrinogen levels, with higher FIBTEM CA5 and MCF levels observed in the CRYO arm during active bleeding. A significant rise in CA5 and MCF values for both FIBTEM and EXTEM measurements was seen between 24 and 72 h in both study arms ( $P < 0.0001$ ), with a greater increase observed in the CRYO group	Curry et al. (2015)
Guided fibrinogen replacement				
Trauma	Single-center, parallel-group, open-label, randomized study of patients with an ISS $> 15$ , bleeding signs, and FIBTEM CA10 $< 9$ mm or EXTEM CT $> 90$ s, randomly treated with FFP ( $n = 48$ ) or CFC (primarily FC, $n = 52$ )	ROTEM analyses were conducted at the ED and ICU and at 24 and 48 h after admission. Patients were randomized to receive FC (CSL Behring, Marburg, Germany) at 50 mg/kg body weight or placebo when FIBTEM CA10 $< 9$ mm or EXTEM CT $> 90$ s	EXTEM CT was shorter in the CFC group. EXTEM $\alpha$ and EXTEM CA10 worsened after FFP treatment, whereas they normalized quickly in patients receiving CFC. FIBTEM CA10 increased insufficiently with FFP, whereas values well above the threshold for transfusion were achieved with CFC. Most of these differences persisted until 24 h after admission, except EXTEM $\alpha$ , which was comparable between the two groups at 24 h after admission	Innerhofer et al. (2017)

(continued)

**Table 4** (continued)

Clinical setting	Study design	Fibrinogen replacement and TEG/ROTEM test	Results	References
	Retrospective, observational study of 96 trauma patients with a median ISS of 34.0 (25.0–44.5) treated with FC only (FC group), FC and PCC (FC + PCC group), or PCC only (PCC group)	Blood samples for ROTEM tests (EXTEM, FIBTEM, and INTEM) were collected as soon as possible following ED admission and during initial operative treatment and ICU stay. Patients with severe coagulopathy upon admission received immediate treatment with both FC (Haemocomplettan P, CSL Behring) (6–8 g) and PCC (20–30 IU/kg body weight). Additional fibrinogen treatment was administered for a FIBTEM CA10 < 7 mm (target FIBTEM CA10: 10–12 mm). If EXTEM CT remained prolonged (>80 s) following FC treatment, PCC (Baxter, Vienna, Austria) was administered	Administration of FC resulted in reductions in EXTEM and FIBTEM CT and an increase in FIBTEM CA10 but had no effect on INTEM CT and CA10 and EXTEM CA10. Combined administration of FC and PCC increased FIBTEM MCF and normalized EXTEM CT but did not change either INTEM or FIBTEM CT. PCC therapy normalized EXTEM and FIBTEM CT and decreased CA10 in EXTEM, INTEM, and	Ponschab et al. (2015)
	Retrospective study of 157 trauma patients with a median ISS of 29, treated with FC alone (FC group), FC and PCC (FC + PCC group), or FC with PCC and FFP (FC + PCC + FFP group)	Blood samples were drawn following ER and ICU admission and at 24 h after admission for EXTEM and FIBTEM tests. FC (Haemocomplettan P) was administered at 2–6 g (2–4 g if initial FIBTEM CA10 = 4–6 mm and 6 g if FIBTEM CA10 = 0–3 mm)	EXTEM CT and CFT in the FC + PCC + FFP group were prolonged upon ICU admission; low MCF and reduced $\alpha$ were also observed in the FC + PCC + FFP group at the same time point. Between-group differences in all EXTEM parameters reached statistical significance upon ER and ICU	Schlimp et al. (2013a)

(continued)

**Table 4** (continued)

Clinical setting	Study design	Fibrinogen replacement and TEG/ROTEM test	Results	References
			admission but not at 24 h FIBTEM CA10 increased between ER and ICU admission in the FC + PCC group but not in either of the other groups. FIBTEM CA10 was lower in the FC + PCC + FFP group than in the other two groups at ICU admission. No between-group differences were observed in any of these parameters at 24 h; all were in the normal range	
	Prospective study of 144 patients with major blunt trauma (ISS > 15) who received FC and/or PCC alone (CF group, $n = 66$ ) and were compared with those additionally receiving FFP transfusions (CF + FFP group, $n = 78$ )	ROTEM was conducted using blood samples collected at ED admission and 4, 6, and 24 h thereafter. FC (Haemocompletan P) was administered at 25–50 mg/kg body weight when fibrinogen <1.5–2.0 g/L, which indicates FIBTEM MCF < 7 mm	CF + FFP patients showed increased FIBTEM MCF at 4, 6, and 24 h when compared with that at ER admission. This group also showed higher FIBTEM MCF at 4 and 6 h than in the CF group	Innerhofer et al. (2013)
	Retrospective study of 131 trauma patients with a mean ISS of $38 \pm 15$ who received $\geq 5$ U of RBC concentrate within 24 h	Blood was drawn immediately after ER and ICU admission. ROTEM tests were performed according to the manufacturer's recommendations within 5 min of blood sampling. When FIBTEM MCF < 10 mm, 2–4 g of FC (Haemocompletan P) was administered.	On ER admission, the mean EXTEM MCF was 50 mm, and the median FIBTEM MCF was 6 mm, which is lower than the normal range (9–25 mm). The median EXTEM CT was 78 s, which is within the normal range (35–80 s). On ICU admission, ROTEM parameter	Schöchel et al. (2010b)

(continued)

**Table 4** (continued)

Clinical setting	Study design	Fibrinogen replacement and TEG/ROTEM test	Results	References
		Patients showing prolonged EXTEM CT (> 1.5 times normal) received an additional 1000–1500 U PCC	values were comparable with preoperative values. Mean plasma fibrinogen was 1.26 g/L on ER admission and 1.50 g/L on ICU admission. The mean fibrinogen level only reached below-normal values 24 h after ER admission (2.28 g/L, normal range – 4.5 g/L)	
	Retrospective, observational study of 36 adult trauma patients with an ISS $\geq$ 15	ROTEM analysis was conducted at ED admission, before and after FC transfusion, after a bleeding episode, and 24–48 h after admission. Median of 22 min (IQR, 17–30 min) from time of FIBTEM CA5 analysis to FC administration. If FIBTEM CA5 $\leq$ 6 mm, an initial dose of 4 g FC was transfused	FIBTEM CA5 and the Clauss fibrinogen level were correlated (correlation coefficients 0.7–0.8), and both were increased significantly ( $p < 0.05$ ) at 24 and 48 h after admission. One gram of FC raised the FIBTEM CA by approximately 1 mm	Seebold et al. (2019)

Abbreviations: *CA* clot amplitude, *CA5* clot amplitude at 5 min after CT measurement, *CA10* clot amplitude at 10 min after CT measurement, *CFC* coagulation factor concentrates, *CPB* cardiopulmonary bypass, *ED* emergency department, *ER* emergency room, *FC* fibrinogen concentrate, *FFP* fresh frozen plasma, *IQR* interquartile range, *MCF* maximum clot firmness, *PC* platelet concentrate, *PC* prothrombin complex concentrate, *ICU* intensive care unit, *ISS* injury severity score, *PC* platelet concentrate, *RBC* red blood cells, *ROTEM* rotational thromboelastometry, *MCF* maximum clot firmness, *TEG* thromboelastography, *FF* functional fibrinogen, *CT* coagulation time, *MHT* major hemorrhage therapy, *PPH* postpartum hemorrhage, *CFT* clot formation time

$p < 0.01$ ), which implied that the test might be profoundly impaired by the incomplete inhibition of platelet contribution to clot strength. Factor XIII levels and platelet count might also affect TEG FF (Gautam et al. 2017; Nielsen et al. 2004). The correlation between FIBTEM CA10 and Clauss fibrinogen became weaker as the hemoglobin level increased, suggesting that the hemoglobin level could influence the measurement of fibrinogen by FIBTEM (Mace et al. 2016). The

correlation could also be weakened by fibrinogen replacement in trauma patients (David et al. 2016).

Hemostatic effects, as measured by TEG and ROTEM, can be affected by resuscitation fluids. Fenger-Eriksen et al. (2010) assessed fibrinogen levels in plasma diluted in vitro with different fluids (isotonic saline, hydroxyethyl starch, human albumin), using an antigen determination method, three photo-optical Clauss methods, one mechanical Clauss method, a prothrombin-derived method, and viscoelastic measurement through ROTEM. Fibrinogen levels were overestimated by the photo-optical Clauss methods due to dilution with hydroxyethyl starch. In contrast, ROTEM FIBTEM MCF was reduced by dilution with hydroxyethyl starch and, to a lesser extent, by dilution with human albumin; the former effect was ascribed to an unexplained interference with the optical source by hydroxyethyl starch, and the latter was due to impairment of fibrin polymerization induced by the fluids. Mittermayr et al. (2007) reported that the magnitude of clot firmness reduction was determined by the type of fluid used in major orthopedic surgery. FIBTEM MCF was most strongly affected by hydroxyethyl starch, followed by gelatin solution and Ringer's lactate solution.

In addition to MA, other TEG parameters, e.g., estimated FLEV, kinetic time K, and  $\alpha$ , and kaolin TEG K and  $\alpha$  can be used to assess fibrinogen levels (Kornblith et al. 2014; Harr et al. 2013). Kornblith et al. (2014) confirmed a significant correlation between TEG FF FLEV and Clauss fibrinogen test in trauma patients, similar to results by Harr et al. (2013). However, the correlations were affected by the fibrinogen level; they decreased at low and high FLEVs (Harr et al. 2013).

In contrast, the FLEV estimated using TEG FF was, on average, 1.0 g/L higher than that determined by the Clauss method in both surgical patients and healthy controls (Fries et al. 2006). This is consistent with other reports of higher TEG FF FLEVs than Clauss values in cardiac surgery (Fries et al. 2005) and obstetric patients (Fenger-Eriksen et al. 2005).

Among all the parameters (kaolin TEG K,  $\alpha$ , and MA), the strongest correlations have been reported between TEG FF MA/ROTEM FIBTEM MCF and the plasma fibrinogen level (Kornblith et al. 2014; Harr et al. 2013), suggesting that these parameters are the most useful for monitoring the role of fibrinogen in the hemostasis of bleeding patients.

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## TEG/ROTEM-Guided Fibrinogen Replacement

ROTEM has been widely used to guide FC administration in different perioperative settings, including trauma surgery, cardiovascular surgeries, and liver transplantation obstetric hemorrhage. Retro- and prospective studies of cardiac surgery have shown that FIBTEM-guided fibrinogen replacement generally reduces transfusion (Williams et al. 2017).

TEG and ROTEM have been mostly implemented during active bleeding situations in the emergency room and during surgery. As summarized in Table 5, case reports (Schöchel et al. 2010c, d; Ziegler et al. 2013; Brenni et al. 2010;

**Table 5** Summary of TEG/ROTEM-guided fibrinogen replacement in trauma

Study design	Guiding protocol for fibrinogen replacement	Main results	References
TEG			
Randomized study of 111 adult trauma patients with a median ISS of 30 (24–43) treated with MTP directed by TEG or SLT	Rapid TEG was performed upon MTP activation on native whole blood within 5 min after collection. If ACT $\geq$ 140 s, 2 U FFP, 10 U of cryoprecipitate, and 1 U PC were transfused; if ACT was 111–139 s, 2 U FFP was transfused; if a $<$ 63°, 10 packs of cryoprecipitate were transfused; if MA $<$ 55 mm, 1 U PC was transfused	Mortality at 28 days was lower in the TEG group than in the SLT group (19.6% vs. 36.4%, $p = 0.049$ ). Less plasma and platelets were required in the TEG group than in the SLT group in the first 2 h of resuscitation	Gonzalez et al. (2016)
Prospective study of 182 adult trauma patients with a median ISS of 17 (9–26) in a level 1 trauma center	Blood was sampled immediately upon admission and was kept at room temperature until analyzed by kaolin and rapid TEG and TEG FF at 1 h after sampling. When TEG FF MA $<$ 14 mm, 20–20 mL FFP/kg body weight, cryoprecipitate pool (3–5 mL/kg) or FC (adults 1–2 g) was transfused	Non-survivors showed lower clot strength by kaolin TEG and TEG FF and lower rapid TEG a and LY30 than survivors. None of the TEG variables were independent predictors of massive transfusion or mortality	Johansson et al. (2013)
Retrospective study of 390 and 442 adult patients (age $\geq$ 15 years) who received more than 10 RBC transfusions within 24 h before and after the implementation of HCR	Kaolin TEG was used during resuscitation and in the operation room and ICU. When $\alpha <$ 52°, 2 U FFP or 1–2 g FC was considered; R = 11–14 min, 2 U FFP or 10 mL FFP/kg body weight was considered; R $>$ 14 min, 4 U FFP, or 20 mL FFP/kg body weight was considered; MA = 46–50 mm, 1 U PC was considered; MA $<$ 46 mm, 2 U PC was considered	PC transfusion within 24 h from admission was increased from 1.7 U to 5 U and 30- and 90-day mortality were reduced from 31.5% to 20.4% and from 34.6% to 22.4%, respectively, as a result of TEG-guided HCR	Johansson and Stensballe (2009)

(continued)



**Table 5** (continued)

Study design	Guiding protocol for fibrinogen replacement	Main results	References
Retrospective study of 165 and 124 trauma patients receiving $\geq 6$ U of RBC within the first 24 h from treatment with TEG-guided or MTP resuscitation, respectively	TEG was performed in the operating room or ICU. If $a < 45^\circ$ , 0.6 U/kg cryoprecipitate; MA = 41–48 mm, 5 U of platelets; MA $\leq 40$ mm, 10 U of platelets were transfused. MTP involved transfusion with a 1:1:1	There were no differences in volumes of blood products or mortality between the two groups. The mortality of the penetrating trauma patients who received $\geq 10$ U RBC decreased from 54.1% for MTP to 33.3% for TEG-directed resuscitation ( $p = 0.04$ )	Tapia et al. (2013)
Case report of trauma patients treated with MTP transfusion, with a 1:1:1 ratio of RBC, FFP, and platelets followed by TEG-guided transfusion	TEG was performed as soon as a blood sample could be obtained. If R $> 8$ min FFP; K $> 4$ min or a $< 47^\circ$ , cryoprecipitate; MA $< 54$ mm, platelets were transfused	TEG allowed for judicious and protocol-assisted utilization of blood components and allowed more effective management of blood products and resuscitation	Walsh et al. (2011)
Retrospective study of 1974 adult patients with a median ISS of 17	Blood was collected on admission and analyzed by rapid TEG. When K $> 2.5$ min or a $< 56^\circ$ or MA $< 55$ mm, cryoprecipitate or FC was transfused (dosage not specified)	Rapid TEG was superior over SLT (PT, PTT, INR, platelet count, and fibrinogen) and identified patients with an increased risk of early RBC, plasma, and platelet transfusions, and fibrinolysis	Holcomb et al. (2012)
Case report of three trauma patients treated with TEG-guided transfusion within MTP	Rapid TEG was performed in the ED. if ACT $> 110$ s, 2 U of FFP; if a $< 63^\circ$ , cryoprecipitate (dosage not specified); MA $< 55$ mm, PC was transfused	TEG-directed therapy showed the potential to be both cost-effective and lifesaving	Sawyer et al. (2012)
Retrospective study of 80 trauma patients with an ISS of $29 \pm 1$	Native whole blood samples were analyzed by rapid TEG with 10 $\mu$ L of rapid TEG solution (8% kaolin, human recombinant tissue factor, phospholipids, buffers, and stabilizers), used as an activator, being added to 0.36 mL of whole blood within 4 min of blood	Clot shear elasticity (G) was an independent predictor of massive transfusion. For the prediction of mortality, G had the greatest adjusted AUC (0.93) compared with the AUCs for base deficit (0.87), INR (0.88), and PTT (0.89)	Pezold et al. (2012)

(continued)

**Table 5** (continued)

Study design	Guiding protocol for fibrinogen replacement	Main results	References
	collection, placed in cuvettes, and warmed to 37.3 °C. if $\alpha < 60$ , cryoprecipitate was transfused		
ROTEM			
Case report of a 52-year-old severely injured male trauma patient who suffered a high-velocity motorcycle accident	ROTEM (EXTEM, INTEM, and FIBTEM) was performed immediately after admission, during surgery, and in the ICU. FIBTEM MCF was 4 mm at admission. Accordingly, 12 g of FC (RiaSTAP/ Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was infused as three doses of 4 g during surgery to increase the FIBTEM MCF to 10 mm. According to FIBTEM MCF = 8 mm at 6 h after ICU admission, another 2 g of FC was administered	EXTEM results showed a slightly prolonged CT of 85 s and reduced MCF of 49 mm at admission. EXTEM CT remained in the normal range throughout the surgical procedure, suggesting normal thrombin generation. On ICU admission, EXTEM revealed CT = 77 s, MCF = 47 mm, and FIBTEM MCF = 13 mm. The patient was fully recovered upon release from the hospital, 60 days after the accident	Schöchli et al. (2010c)
Case report of a 7-year-old boy with severe abdominal and pelvic injuries	Immediately on ED admission and 1 and 2 h into surgery, blood samples were taken for EXTEM and FIBTEM. One unit of RBC concentrate (250 mL), 0.5 g of FC (Haemocomplettan P), and 250 mL of crystalloid were administered on ED admission. When FIBTEM MCF = 9 mm at 1 h, 0.5 g of FC was transfused; when FIBTEM MCF = 8 at 2 h, 1 g of FC was administered	FFP and PC transfusions were avoided, showing the application potential of preemptive fibrinogen supplementation followed by a goal-directed, theragnostic approach to hemostatic therapy in pediatric trauma	Ziegler et al. (2013)

(continued)

**Table 5** (continued)

Study design	Guiding protocol for fibrinogen replacement	Main results	References
Case report of a 24-year-old man with a severe blunt abdominal trauma	ROTEM FIBTEM was performed 30 min after hospital admission indicating afibrinogenemia, and 4 g of FC (Haemocomplettan P) was intravenously administered. FIBTEM was performed 1 h after admission due to persistent afibrinogenemia, and an additional 8 g of FC was administered, followed by administration of 4 g of FC 1 h later, resulting in normal FIBTEM	ROTEM-guided FC treatment was successful and avoided FFP and platelet transfusions. ROTEM provided better guidance than INR and PTT for treatment decisions	Brenni et al. (2010)
Case report of a 68-year-old male patient with serious craniofacial trauma and massive hemorrhage	A blood sample was taken for ROTEM analysis (EXTEM, FIBTEM) on ED admission. EXTEM CT and CFT were prolonged by 167 and 739 s, respectively; MCF was below normal, at 29 mm. FIBTEM CA10 was only 2 mm, and a shorter clotting time was observed in APTEM than in EXTEM. Tranexamic acid (2 g) was administered to correct fibrinolysis. The patient was then treated with 1000 IU PCC (Uman complex DI), 5 g FC (Haemocomplettan P), and 2 U of PC	The patient's coagulation was normalized 2 h after admission in terms of EXTEM CT (62 s), MCF (50 mm), and FIBTEM MCF (10 mm), suggesting the success of ROTEM-guided CFC therapy for massive hemorrhage associated with craniofacial injury	Grassetto et al. (2012)
Retrospective study of 681 trauma patients with an ISS $\geq$ 16, AIS for thorax and/or abdomen and/or extremity $\geq$ 3, and AIS for head/neck $<$ 5	ROTEM analyses were performed on ED and ICU admission. Hemostatic therapy consisted of administration of 2–4 g of FC (Haemocomplettan P, CSL Behring GmbH,	RBC transfusion was avoided in 29% of patients in the FC-PCC group compared with only 3% in the FFP group ( $p < 0.001$ ). PC transfusion was avoided in 91% of patients in the FC-PCC group	Schochl et al. (2011)

(continued)

**Table 5** (continued)

Study design	Guiding protocol for fibrinogen replacement	Main results	References
	Marburg, Germany) when FIBTEM MCF < 10 mm and administration of 1000–1500 IU of PCC for patients showing prolonged EXTEM CT (>1.5 times normal)	compared with 56% in the FFP group ( $p < 0.001$ ). Mortality was comparable between the two groups: 7.5% in the FC-PCC group and 10.0% in the FFP group ( $p = 0.69$ )	
Retrospective study of 131 trauma patients with a mean ISS of $38 \pm 15$ who received $\geq 5$ U of RBC concentrate within 24 h	Blood was drawn on ED and ICU admission for ROTEM analysis, per the manufacturer's recommendations, and the analyses were started within 5 min of blood sampling. When FIBTEM MCF < 10 mm, 2–4 g of FC (Haemocomplettan P) was administered. Patients showing prolonged EXTEM CT (>1.5 times normal) received an additional 1000–1500 IU PCC	The observed mortality was 24.4% lower than the TRISS mortality of 33.7% ( $p = 0.032$ ) and the RISC mortality of 28.7% ( $p > 0.05$ ). After excluding 17 patients with traumatic brain injury, the difference in mortality was 14% observed vs. 27.8% predicted by TRISS ( $p = 0.0018$ ) and 24.3% predicted by RISC ( $p = 0.014$ ). These results supported ROTEM-guided hemostatic therapy, with FC as a first-line hemostatic therapy	Schöchl et al. (2010b)
Prospective study of 144 patients with major blunt trauma (ISS > 15). Patients who received FC and/or PCC alone (CF group) were compared with those who additionally received FFP transfusion	ROTEM was conducted with blood samples collected at ED admission and 4, 6, and 24 h thereafter. FC (Haemocomplettan P) was administered to correct low fibrinogen level and/or poor fibrin polymerization (fibrinogen level < 1.5–2.0 g/L, which equals FIBTEM MCF < 7 mm) at 25–50 mg/kg body weight	Patients treated with CF alone showed sufficient hemostasis and received significantly fewer units of RBC and platelets than those in the FFP group. Fewer patients developed MOF or sepsis in the CF group than those in the FFP group. Propensity score matching ( $n = 28$ pairs) used to reduce the impact of treatment selection confirmed that additional FFP administration showed no benefit in restoring hemostasis but was associated with higher RBC and platelet transfusion rates	Innerhofer et al. (2013)

(continued)

**Table 5** (continued)

Study design	Guiding protocol for fibrinogen replacement	Main results	References
Retrospective study of 157 trauma patients with a median ISS of 29 treated with FC alone (FC group), FC and PCC (FC + PCC group), or FC with PCC and FFP (FC + PCC + FFP group)	Blood samples for EXTEM and FIBTEM tests were drawn on ED admission. FC (Haemocomplettan P) was administered at 2–6 g (2–4 g if initial FIBTEM CA10 was 4–6 mm; 6 g if initial FIBTEM CA10 was 0–3 mm)	Plasma fibrinogen levels were maintained within the normal range in all patient groups. Transfusion requirements were the highest in the FC + PCC + FFP group and the lowest in the FC group	Schlimp et al. (2013a)
Prospective, observational, descriptive study of 77 trauma patients, with a mean ISS score of 25.6, separated into three cohorts: Patients who received no coagulation therapy (NCT group), patients treated with FC only (FC group), and patients treated with both FC and PCC (FC + PCC group)	ROTEM tests (EXTEM, FIBTEM, and INTEM) were performed on ED admission, during initial operative treatment and ICU stay and every morning thereafter, up to day 7. For patients with obviously severe coagulopathy upon admission, both FC (Haemocomplettan P) (6–8 g) and PCC (20–30 IU/kg body weight) were immediately administered. Additional fibrinogen was administered when FIBTEM CA10 was 0–3 mm, 6 g FC, and when FIBTEM CA10 was 4–6 mm, 3–4 g FC, to target 10–12 mm. If EXTEM CT remained prolonged (> 80 s) following FC treatment, PCC (Baxter, Vienna, Austria) was administered	ETP was higher in the FC + PCC group than that in the NCT group on days 1–4 and that in the FC group on days 1–3. Fibrinogen increased over time, with no significant between-group differences after ER admission. PT and PTT were prolonged in the FC + PCC group from admission until day 3–4	Schöchli et al. (2014)
Retrospective observational study of 96 trauma patients with a median ISS of 34.0 (25.0–44.5) treated with FC only (FC group), FC and PCC (FC + PCC group), or PCC only (PCC group)		Administration of FC resulted in reductions in EXTEM and FIBTEM CT and an increase in FIBTEM CA10 but had no effect on INTEM CT, CA10, and EXTEM CA10. Combined administration of FC and PCC increased FIBTEM MCF and normalized EXTEM CT but did not affect INTEM or FIBTEM CT. PCC therapy normalized EXTEM and FIBTEM CT and decreased CA10 in EXTEM, INTEM, and FIBTEM	Ponschab et al. (2015)
Retrospective observational study of 435 trauma patients treated with (treatment group) or without (control group) FC		In the treatment group (median FC dose 6 g), the fibrinogen level was lower than that in the control group on admission and up to	Schlimp et al. (2016)

(continued)

**Table 5** (continued)

Study design	Guiding protocol for fibrinogen replacement	Main results	References
		day 2. In patients receiving high ( $\geq 10$ g) doses of FC, the fibrinogen level was lower up to day 5 than that in the control group. At other time points, there was no difference between the groups	
Retrospective, observational study of 36 adult patients with ISS $\geq 15$	ROTEM analysis was conducted at various time points from ED admission to 48 h after admission. FIBTEM CA5 < 10 mm in the setting of significant hemorrhage triggered fibrinogen replacement with FC	The median time from FIBTEM CA5 analysis to FC administration was 22 min (IQR, 17–30 min). The FIBTEM CA5 and Clauss fibrinogen levels were correlated (spearman correlation coefficient, 0.7–0.8), and both were significantly increased ( $p < 0.05$ ) by 24 h after admission	Seebold et al. (2019)
Randomized-controlled trial of 100 trauma patients with ISS > 15 treated with FFP (15 mL/kg body weight, $n = 48$ ) or CFC (primarily FC) (50 mg/kg body weight, $n = 52$ )	ROTEM analyses were conducted at the ED, at 24 h at the ICU. Patients received FC (CSL Behring, Marburg, Germany) at 50 mg/kg body weight when FIBTEM CA10 < 9 mm and four-factor PCC at 20 IU/kg body weight when EXTEM CT > 90 s or prothrombin time index < 35%	A higher proportion of patients in the FFP group required rescue therapy than that in the CFC group (52% vs. 4%, $p < 0.0001$ ) and had an increased need for massive transfusion (30% in the FFP group vs. 12% in the CFC group, $p = 0.042$ ) than that in the FFP group. There was no difference in MOF between the two groups	Innerhofer et al. (2017)

Abbreviations: *AIS* abbreviated injury scale, *AUC* area under the curve, *CA5* clot amplitude at 5 min after CT measurement, *CA10* clot amplitude at 10 min after CT measurement, *CFC* coagulation factor concentrates, *CPB* cardiopulmonary bypass, *CT* clotting time, *ICU* intensive care unit, *ED* emergency department, *FC* fibrinogen concentrate, *FFP* fresh frozen plasma, *HCR* hemostatic control resuscitation, *INR* international normalized ratio, *MCF* maximum clot firmness, *MOF* multiorgan failure, *MTP* massive transfusion protocol, *PC* platelet concentrate, *PCC* prothrombin complex concentrate, *PT* prothrombin time, *PTT* partial thromboplastin time, *RBC* red blood cell, *RISC* revised injury severity classification, *ROC* receiver operating characteristics, *SLT*, standard laboratory test, *TRISS* trauma injury severity score, *ROTEM* rotational thromboelastometry, *CFT* clot formation time, *ISS* injury severity score, *ETP* endogenous thrombin potential, *ED* emergency department, *IQR* interquartile range, *TEG* thromboelastography, *ACT* activated clotting time, *FF* functional fibrinogen

Grassetto et al. 2012), retrospective (Ponschab et al. 2015; Schlimp et al. 2013a, 2016; Schöchel et al. 2010b, 2011; Seebold et al. 2019) and prospective clinical studies (Innerhofer et al. 2013; Schöchel et al. 2014), and randomized controlled trials (Innerhofer et al. 2017) have demonstrated that ROTEM FIBTEM has been successfully used to guide fibrinogen administration in trauma, leading to reduced allogeneic blood transfusion (Innerhofer et al. 2013; Ziegler et al. 2013; Schöchel et al. 2010d).

In contrast, there are few studies on TEG-guided fibrinogen replacement across various clinical settings, with most focusing on trauma. Kaolin-activated TEG (Johansson and Stensballe 2009; Tapia et al. 2013; Walsh et al. 2011) and rapid TEG (Gonzalez et al. 2016; Holcomb et al. 2012; Sawyer et al. 2012; Pezold et al. 2012) rather than TEG FF were used to guide fibrinogen supplementation in these studies, and TEG  $\alpha$  was used to guide fibrinogen supplementation, whereas MA was used to guide platelet transfusion. Some of these studies used FFP (Johansson and Stensballe 2009) and cryoprecipitate transfusion guided by TEG (Walsh et al. 2011; Pezold et al. 2012) instead of FC. Disadvantages of FFP and cryoprecipitate include the requirement for cold storage and time for thawing (17 min on average) (Curry et al. 2015), risk of viral transmission, and large administration volume. FFP contains a low fibrinogen level, which can vary greatly between batches, and, when administered in large volumes, may dilute plasma fibrinogen (McNamara et al. 2015).

The clinically best-studied FCs in the USA and Canada are Haemocomplettan P and RiaSTAP (CSL Behring GmbH, Marburg, Germany); other commercially available FC products include Clottagen (LFB Biomédicaments, Les Ulis, France) (Rouillet et al. 2015), Fibrinogen HT (Benesis, Osaka, Japan), and FibroRAAS (Shanghai RAAS, Shanghai, China) (Franchini and Lippi 2012). Fibryga (Octapharma, Lachen, Switzerland) is a new, highly purified, lyophilized FC (Schulz et al. 2018). In vitro and clinical studies have shown a higher factor XIII level (10.1 IU/mL vs. 7.2 IU/mL) (Haas et al. 2018), slower clearance (0.665 mL/h/kg vs. 0.804 mL/h/kg), and a larger volume of distribution (70.158 mL/kg vs. 76.631 mL/kg) for Fibryga than for RiaSTAP (Ross et al. 2018). Another clinical study reported an even lower clearance (0.53 mL/h/kg) and lower distribution volume (50.7 mL/kg) for Clottafact (Djambas Khayat et al. 2019).

While FC is generally administered by bolus intravenous injection, one study showed potential advantages of using continuous infusion, as it allows rapid adjustments in the delivery rate in response to changing plasma levels (Morrison et al. 2012). It avoids or reduces peaks and troughs in the plasma fibrinogen level and allows the maintenance of satisfactory hemostasis during surgery.

Different critical fibrinogen levels and cutoff values for TEG and ROTEM have been used to guide fibrinogen replacement therapy in trauma (Theusinger et al. 2014; Mengoli et al. 2017; Nardi et al. 2015; Schöchel et al. 2012, 2013b; Fries et al. 2009; Lier et al. 2013; Görlinger et al. 2012) (Table 6). Most of these thresholds are parts of the ROTEM- or TEG-guided transfusion algorithms for different blood products (RBC, FFP, platelets) (Johansson et al. 2013; Stensballe et al. 2014; Johansson et al. 2014). Fibrinogen supplementation has been recommended for a plasma fibrinogen level below 1 g/L (Miceli et al. 2016), which approximately corresponds to a TEG

**Table 6** Summary of threshold values for TEG- and ROTEM-guided fibrinogen replacement in trauma

Triggers	Fibrinogen dosage	References
FIBTEM MCF < 7 mm, which equals fibrinogen level < 1.5–2.0 g/L	25–50 mg/kg BW	Innerhofer et al. (2013)
FIBTEM MCF < 10 mm	2–4 g	Schöchgl et al. (2010b, 2011)
FIBTEM CA5 = 4–6 mm FIBTEM CA5 = 2–4 mm FIBTEM CA5 < 2 mm	25 mg/kg BW 50 mg/kg BW 75 mg/kg BW	David et al. (2016)
FIBTEM CA10 < 7 mm	3–8 g	Schöchgl et al. (2014)
Blood loss >50% with diffuse bleeding and FIBTEM MCF ≤ 7 mm	Fibrinogen 2–4 g (maximally 3 × 2 g), after 6 g fibrinogen factor XIII was administered	Theusinger et al. (2014)
Blood loss >60% with ongoing diffuse bleeding, EXTEM/INTEM CT normal, MCF < 40 mm, and FIBTEM MCF < 7 mm	Fibrinogen up to 6 g, followed by factor XIII 15 U/kg BW	
FIBTEM CA10 ≤ 7 mm	2–4 g	Nardi et al. (2015)
FIBTEM CA10 = 0–3 mm FIBTEM CA10 = 4–6 mm	6 g 2–4 g Until FIBTEM CA10 = 10–12 mm	Schöchgl et al. (2013a, b), Schlimp et al. (2013a)
FIBTEM CA10 < 7 mm	2–6 g until FIBTEM CA10 = 10–12 mm	Schöchgl et al. (2012)
EXTEM CA10 < 45 mm and FIBTEM CA10 < 15 mm	2–6 g	Lier et al. (2013)
FIBTEM CA5 < 5 mm with bleeding or ongoing surgery and FIBTEM CA20 < 10 mm	50 mg/kg BW	Fries et al. (2009)
TEG FF MA < 14 mm	1–2 g	Johansson et al. (2013, 2014)
Rapid TEG K > 2.5 min, α < 56°	Unspecified	
TEG FF MA 7–14 mm TEG FF MA 0–7 mm	20 mg/kg BW 30 mg/kg BW	Stensballe et al. (2014)
FIBTEM MCF 6–9 mm FIBTEM MCF 0–6 mm	20 mg/kg BW 30 mg/kg BW	
EXTEM CA10 < 40 mm and FIBTEM CA10 < 10 mm	20–50–100 mg/kg BW	Görlinger et al. (2012)

Unless specified otherwise, TEG 5000 and ROTEM delta were used to guide fibrinogen replacement

Abbreviations: *BW* body weight, *CA* clot amplitude, *CA5/10/20* clot amplitude at 5/10/20 min after CT measurement, *MCF* maximum clot firmness, *CT* coagulation time, *TEG* thromboelastography, *K* kinetic time, *a* angle, *FF* functional fibrinogen, *MA* maximum amplitude

FF MA of 16 mm and ROTEM FIBTEM MCF of 8 mm (Peng et al. 2019). The abovementioned values of TEG FF MA and ROTEM FIBTEM MCF are both higher than the lower thresholds of the normal ranges for the TEG FF (11–24 mm) and



ROTEM FIBTEM (7–24 mm) tests recommended by the respective manufacturers. This agrees with a report that the frequently recommended threshold for fibrinogen substitution of 9 mm MCF in FIBTEM does not match the recommended threshold of  $\leq 1.0$  g/L plasma fibrinogen measured by the Clauss method, although there was a strong correlation between FIBTEM MCF and Clauss fibrinogen ( $r > 0.8$ ) (Requena et al. 2011). These discrepancies should be considered carefully when developing goal-guided fibrinogen replacement using TEG and ROTEM.

Fibrinogen levels of 0.8–2.0 g/L have been recommended as transfusion triggers in trauma and massive hemorrhage (Levy et al. 2014; Kaufner et al. 2016), with a level of 1 g/L being reported in most guidelines for fibrinogen replacement (McQuilten et al. 2017b). Accordingly, a range of CA10 and MCF values in FIBTEM, including CA10  $< 7$  mm (target FIBTEM CA10: 10–12 mm) (Ponschab et al. 2015; Schöchel et al. 2012) or MCF  $< 7$  mm in trauma (Innerhofer et al. 2013), CA  $< 8$  mm in cardiac surgery (Weber et al. 2014), and MCF  $< 8$  mm in liver transplantation (Goerlinger 2006), have been used to trigger fibrinogen replacement. Moreover, FIBTEM CA10 or MCF can be used to determine the FC dosage. For example, 2–4 g FC was required in trauma patients if FIBTEM CA10 was 4–6 mm; and 6 g FC was required if FIBTEM CA10 was 0–3 mm (Schlimp et al. 2013a). FC administration has also been based on the plasma fibrinogen level, with varying thresholds (Weiss et al. 2011; Danés et al. 2008). Specifically, the fibrinogen dosage can be calculated based on the desired increment in fibrinogen level, as follows (Lier et al. 2013):

$$\text{Fibrinogen dosage (g)} = 0.05 \times \text{desired increment} \left( \frac{\text{g}}{\text{L}} \right) \times \text{body weight (kg)}$$

There are fewer studies on TEG-guided fibrinogen transfusion in trauma (Gonzalez et al. 2016; Holcomb et al. 2012; Johansson and Stensballe 2009; Tapia et al. 2013; Walsh et al. 2011; Pezold et al. 2012). Compared with ROTEM FIBTEM, TEG FF, which uses a platelet inhibitor, has been less employed to measure fibrinogen levels and guide its administration. TEG FF MA  $< 14$  mm has been used to trigger fibrinogen supplementation in patients with massive hemorrhage (Johansson et al. 2014), and MA  $\leq 7$  mm has been used in liver transplantation (De Pietri et al. 2016). Kaolin or rapid TEG K and  $\alpha$  has been used to guide fibrinogen supplementation with cryoprecipitate in trauma (Schöchel et al. 2013a; Tapia et al. 2013; Brazzel 2013; Gonzalez et al. 2010; Stahel et al. 2009; Kashuk et al. 2009, 2012), but may not be as good as TEG FF MA, which is a more direct measure of the plasma fibrinogen level (Harr et al. 2013; Solomon et al. 2015).

Compared with ROTEM MCF, TEG  $\alpha$ , in particular, kaolin-activated TEG  $\alpha$ , is most commonly used to guide fibrinogen replacement (mostly using a cryoprecipitate), whereas TEG MA is generally used to guide platelet transfusion (Solomon et al. 2015). However, TEG MA could not distinguish fibrinogen from platelet deficiency when a single TEG test was conducted without platelet inhibitors; thus, its use in guiding fibrinogen transfusion may be limited (Kashuk et al. 2012).

These results underline the necessity to implement different individual triggers for fibrinogen supplementation, depending on the viscoelastic hemostatic tests used and the clinical settings. For example, in bleeding trauma patients, a FIBTEM CA10  $\leq 7$  mm may trigger FC administration, with a target MCF of 10–12 mm. In contrast, when using TEG FF, MA  $< 14$  mm is recommended as a trigger (Schochl et al. 2016).

Cutoff values of kaolin TEG K  $> 2.4$  min,  $\alpha < 60.6^\circ$ , and MA  $< 51.2$  mm have been recommended for the diagnosis and treatment of severe hypofibrinogenemia (fibrinogen  $< 1$  g/L) in trauma patients, whereas K could be used to guide early cryoprecipitate or FC transfusion (Chow et al. 2019).

One study suggested that the CA 10 min after R or CT reflects a more dynamic phase of the hemostatic process than MA/MCF and may lead to earlier goal-directed transfusion therapy (Meyer et al. 2014). FIBTEM and APTTEM have been used in combination with EXTEM to guide platelet transfusion and the treatment of hyperfibrinolysis with tranexamic acid (Smith et al. 2020; Juffermans et al. 2019), respectively.

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## Mini-Dictionary of Terms

- *Trauma-induced coagulopathy (TIC). TIC normally refers to acute traumatic coagulopathy which consists of two core components: (1) trauma itself, tissue damage- and hypoperfusion-induced endogenous TIC and (2) resuscitation-associated exogenous TIC involving hypothermia, acidosis, and hemodilution.*
- *Viscoelastic hemostatic tests. These tests measure changes in viscoelastic properties of whole blood during clot formation, buildup, and degradation. The most commonly used devices are thrombelastography (TEG 5000) and rotational thromboelastometry (ROTEM delta).*
- *Conventional coagulation tests (CCTs). These tests also refer to standard laboratory tests typically including prothrombin time (PT) and activated partial thromboplastin time (aPTT), Clauss fibrinogen test, and platelet count.*
- *Fibrinogen concentrate. It is plasma-derived, highly purified concentrate of lyophilized human fibrinogen and needs to be reconstituted with sterile water for infusion.*
- *Hypofibrinogenemia. It is normally defined as plasma fibrinogen concentration below 1.5 g/L.*
- *Fibrinogen replacement. It is treatment of fibrinogen deficiency with exogenous fibrinogen via infusion of fibrinogen concentrate or cryoprecipitate.*

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## Key Facts of Trauma

- *Trauma is a major global public health issue, causing nearly six million deaths worldwide each year.*

- *It is the leading cause of death in people aged 18–39 years.*
- *Hemorrhage is the most common cause of preventable deaths after trauma.*

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## Summary Points

- *TEG and ROTEM tests play important roles in early diagnosis of TIC and its phenotypes, assessment, and guidance of fibrinogen replacement. Their potential clinical benefits are often inferred from trauma and cardiac surgery literature.*
- *ROTEM FIBTEM MCF has been mostly used to discriminate fibrinogen deficiencies and assess hemostatic effects of fibrinogen replacement compared to kaolin and rapid TEG, and TEG FF parameters including K,  $\alpha$ , and MA.*
- *When using TEG FF and ROTEM FIBTEM to diagnose fibrinogen deficiency and guide fibrinogen administration, other variables, such as hematocrit, factor XIII levels, resuscitation fluids, and fibrinogen level ranges, should be considered.*
- *Since TEG FF and ROTEM FIBTEM test results have shown the strongest correlation with plasma fibrinogen level and provided the greatest discrimination of fibrinogen deficiencies, these tests are recommended for guiding fibrinogen replacement and monitoring its hemostatic effects.*
- *Studies comparing TEG FF and ROTEM FIBTEM suggest a stronger correlation of the latter with the plasma fibrinogen level, likely owing to its more effective elimination of the platelet contribution to clot strength.*
- *Studies supporting the use of TEG FF and ROTEM FIBTEM are limited to trauma and surgical bleeding patients. Even without robust clinical data, TEG and ROTEM are likely to remain popular for the hemostatic management of bleeding patients.*
- *Future studies comparing the different intervention thresholds for TEG and ROTEM and the therapeutic effects of predefined thresholds for fibrinogen augmentation are required to optimize fibrinogen administration (i.e., dosage and time of fibrinogen administration) to improve its efficacy and patient safety and to reduce costs in various clinical settings. Studies comparing preemptive and guided fibrinogen replacement are also warranted.*

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