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The Utility Of Thromboelastography In Acute Perioperative Trauma Resuscitation Of The Adult Coagulopathic Patient

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Scholarly Project

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Abstract

One quarter of all patients admitted to level I trauma centers receive transfused blood, and approximately 25% of trauma transfusion recipients are diagnosed with coagulopathies during the resuscitation process (Hess et al., 2008; Kutcher & Cohen, 2021; Maegele et al., 2007). Such pathologies have been associated with negative clinical outcomes such as increased transfusion requirements, organ failure, sepsis, and death. (Barash et al., 2013; Cole et al., 2019; Hess et al., 2008; Sayce et al., 2020). Current laboratory standards of care to diagnose coagulopathies such as prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) are time consuming to obtain and may not reflect a trauma patient's ongoing coagulation status (Baksaas-Aasen et al., 2020; Barash et al., 2013; Davenport et al., 2011). Consequently, point-of-care tests of hemostatic function such as thromboelastography (TEG) may be of use to the anesthesia provider.

An examination of the history of TEG, review of the current literature, and analysis of future research directions has revealed certain limitations such as a potentially extensive clinician learning curve, minimal integration into existing hospital structures, and a lack of level-1 evidence. However, thromboelastography has the potential to optimize outcomes in the coagulopathic patient when used in conjunction with conventional coagulation tests—providing a complementary real-time graphic depiction of the poorly understood syndrome of trauma induced coagulopathy.

Keywords: trauma, coagulopathy, thromboelastography, transfusion

The Utility of Thromboelastography in Acute Perioperative Trauma Resuscitation of the Adult Coagulopathic Patient

Trauma is the number one cause of death for all individuals below the age of 45 in the United States (Center for Disease Control and Prevention & National Center for Health Statistics, 2021), and the fourth leading cause of death for Americans of all ages (Trauma Facts and Links, 2020). Unfortunately, worldwide deaths from traumatic injury are predicted to increase over the next decade despite advances in medical and surgical resuscitation (Asehnoune et al., 2017; Mathers & Loncar, 2006; Sakran et al., 2012; Trauma Facts and Links, 2020).

Up to 25% of trauma patients receive transfused blood products upon hospital admission, and approximately one quarter are also diagnosed with coagulopathies during the resuscitation process (Hess et al., 2008; Kutcher & Cohen, 2021; Maegele et al., 2007). Hemostatic dysfunction related to major trauma is often attributed to trauma induced coagulopathy (TIC), a poorly understood syndrome (Baksaas-Aasen et al., 2019; Meledeo et al., 2017). Trauma induced coagulopathy has been associated with negative clinical outcomes such as increased transfusion requirements, organ failure, sepsis, and death. (Barash et al., 2013; Cole et al., 2019; Hess et al., 2008; Sayce et al., 2020).

Standard monitoring tests, also known as conventional coagulation tests (CCTs), have a turnaround time of between 30 minutes and up to four hours (Toulon et al., 2009); this is often too slow to properly assess and treat evolving coagulopathies (Baksaas-Aasen et al., 2020; Barash et al., 2013; Davenport et al., 2011). Therefore, established viscoelastic testing technologies such as thromboelastography (TEG) may be of benefit to the anesthesia provider as they have the potential for real-time analysis of the dynamic syndrome of TIC. This paper will serve as an examination of the history of thromboelastography, a comprehensive literature

review of its utility in acute perioperative trauma resuscitation of the adult coagulopathic patient, and a discussion of TEG's future applications and further directions.

Background

History of Thromboelastography

TEG was developed in 1948 at the Heidelberg University School of Medicine in Germany (Hartert, 1948). Originally utilized for research purposes, the first clinical mention of TEG outside Europe was in a 1958 University of Colorado paper authored by now well-known cardiac surgeon Henry Swan (Von Kaulla & Swan, 1958). In his research, Swan utilized TEG to assess fibrinolysis during pump-oxygenated open-heart surgery. In the 1960s, TEG began to be used during liver transplantation (Kang et al., 1985; Von Kaulla et al., 1966) and continues to be used as a part of both surgeries today as an intraoperative guide and postoperative measure of bleeding (Gibbs et al., 1994; Tuman et al., 1989). One of the first mentions of TEG's use specific to trauma was in the 1990s by Kaufmann et al. (1997), where the authors found the test to be an indicator of coagulation abnormalities and subsequent transfusion requirements in blunt trauma patients. Viscoelastic monitoring is now part of the American College of Surgeons' Advanced Trauma Life Support recommendations and is suggested in all Level 1 and 2 trauma centers throughout the United States (American College of Surgeons Committee on Trauma, 2018). However, while this technology is recommended, only 9-18% of centers have currently incorporated TEG into their trauma transfusion algorithms (American College of Surgeons Committee on Trauma, 2018; Sayce et al., 2020).
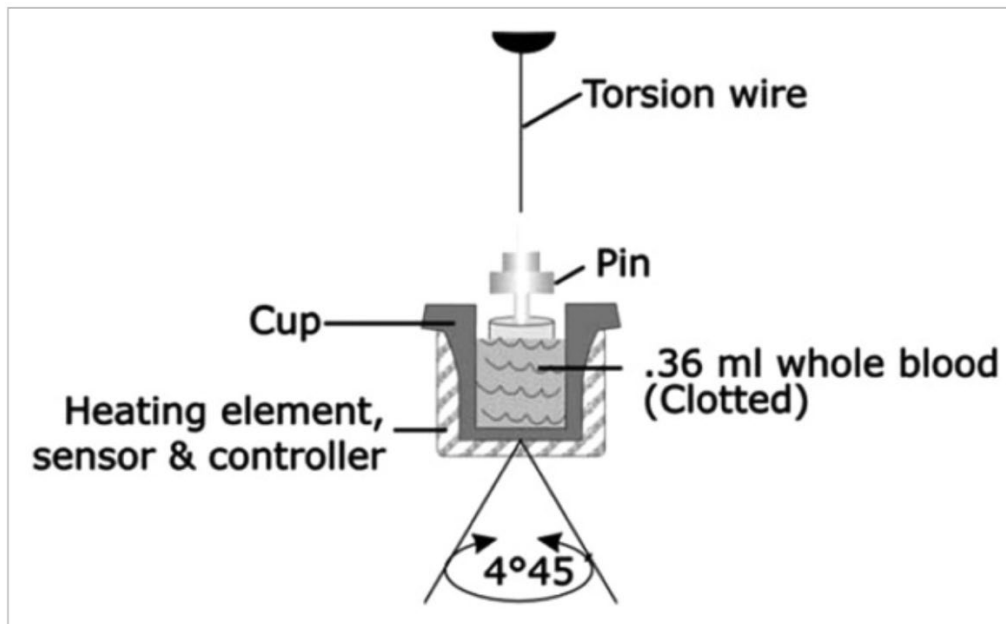
Technology

TEG provides a real-time measurement of the blood's ability to form a clot. It displays a timeframe of clot formation while quantifying the dynamic physiological changes that occur

during the clotting process. The test takes place within a system known as a

'thromboelastograph' which contains a cup heated to 37 degrees centigrade (body temperature)

with a pin suspended in its center. Measurement begins when a small whole blood sample is

placed in the cup which then mechanically oscillates around the detection pin. As a clot forms,

blood viscosity increases, and the pin begins to move with the sample. This increase in torque is

sensed by an electromagnetic inducer and a visual representation of the pin's motion in relation

to time is transduced and analyzed via software (Brill et al, 2021).

There are newer versions of this technology that utilize vibration instead of cup

oscillation, as well as variations in the reagents added to the blood, however the principle of a

transduction of the clot's developing fibrin mesh and platelet onto a 2-D tracing is still the same

(Shaydakov, 2022). The basic mechanics of TEG are summarized below (Figure 1).

Figure 1

Whiting & Dinardo's Depiction of TEG Mechanism

Note: This figure was published by Whiting & Dinardo in 2014 in an article describing the technology and clinical applications of TEG and ROTEM. From Whiting, D., & DiNardo, J. A. (2014). TEG and ROTEM: Technology and clinical applications. *American Journal of Hematology*, *89*(2), 228–232. https://doi.org/10.1002/ajh.23599

Specimen Collection

Thromboelastogram analysis begins with blood sample collection. A venous sample is placed in a plastic vial containing 3.2% buffered sodium citrate (Shaydakov, 2022). Citrate binds calcium, a coagulation co-factor, and prevents blood from clotting before the test can be run (Barash et al., 2013). The in-vial citrate to blood ratio goal is 1:9 and the samples collected are viable for up to two hours at room temperature (Shaydakov, 2022). Whole blood with no additives can also be utilized, but TEG analysis must be conducted immediately (Sayce et al., 2020; Shaydakov, 2022).

Once a specimen has been obtained, 340 microliters (0.34 milliliters) is pipetted into the

TEG cup and re-calcified via the addition of 0.2 mL calcium chloride. A kaolin-cephalin reagent

is then added to activate the sample (Sayce et al., 2020; Shaydakov, 2022). Kaolin is a mineral

composed of hydrated aluminum silicate. It is a negatively charged molecule and serves to

initiate the intrinsic coagulation pathway via activation of factor XII (Barash et al., 2013; Brill et.

al, 2021; Sayce et al., 2020; Shaydakov, 2022). Cephalins, also known as

phosphatidylethanolamines, are a class of phospholipids that are present in human cell

membranes and act as an important co-factor in the coagulation cascade (Barash et al., 2013;

Shaydakov, 2022). Cephalins enable tenase and prothrombinase complexes on the surface of

platelets, which then allows for the generation of thrombin (Barash et al., 2013; Shaydakov,

2022). Thrombin can then convert fibrinogen to fibrin, which forms the architecture of a

developing clot (Barash et al., 2013).

The physiology of the human clotting cascade is still an active area of research and while

an in-depth analysis is beyond the scope of this paper, a brief summary is represented in Figure

2. The importance of calcium is evident throughout the common and intrinsic pathway, as is the

conversion of fibrinogen to fibrin in developing the clot.

Figure 2.

The Classical Coagulation Cascade
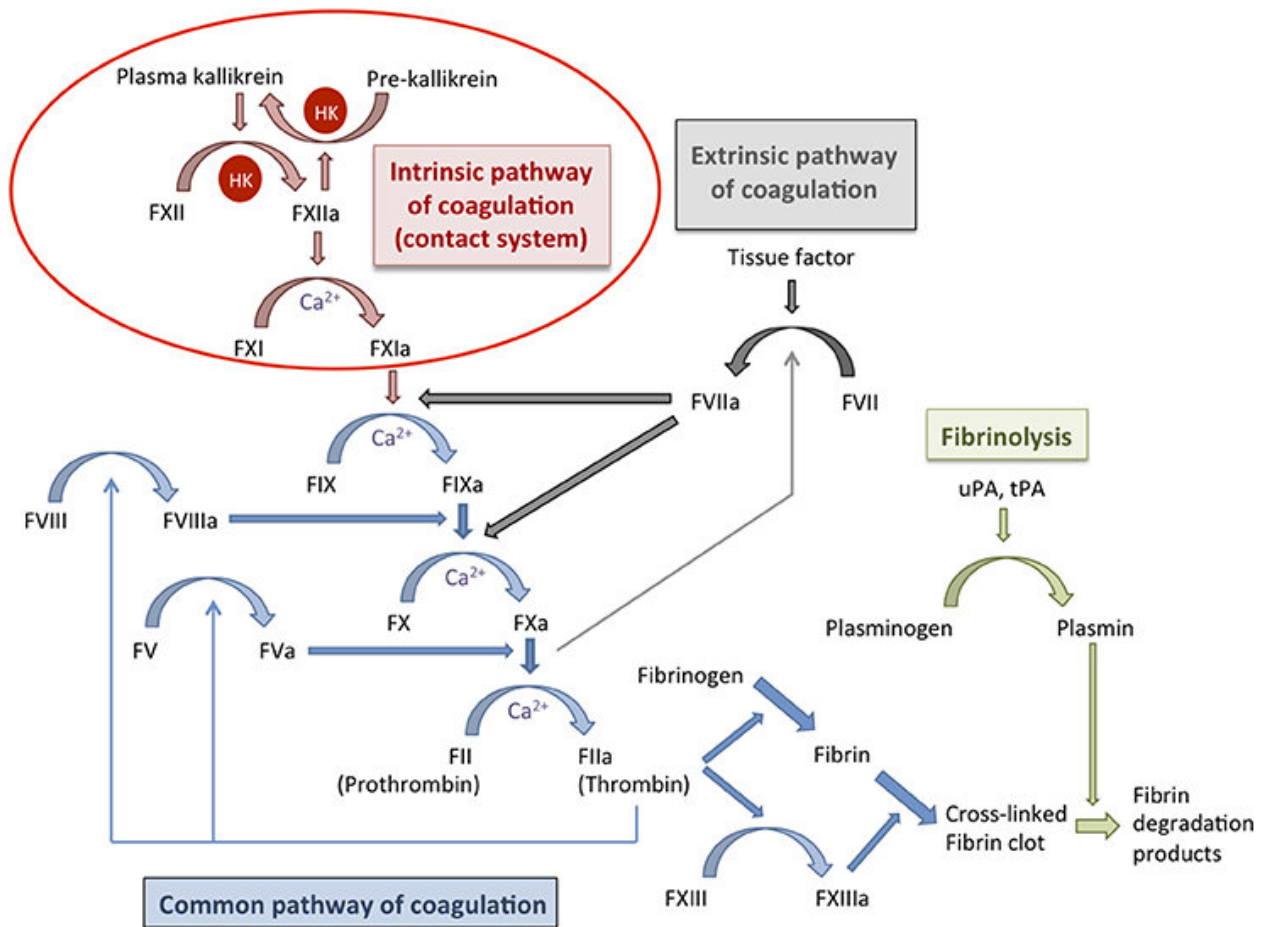
Note: This image is publicly licensed under creative commons 4.0. Of note, the 'classical' version of the clotting cascade depicted in this picture has largely been replaced by the 'cell-based' model of hemostasis, however, it was the dominant theory at the time of TEG development and use and still provides a good reference framework (Barash et al., 2013; *Coagulopathy in Trauma Patients*, 2021).

TEG Tracing Interpretation

A traditional TEG tracing consists of an X and Y axis. The X-axis is representative of time, while the Y-axis is representative of the torque/resistance to oscillation of the forming clot (Brill et al, 2021). A simplified depiction of this diagram in relation to the physiologic process of clot formation is presented in Figure 3 (*TEG 5000 Hemostasis Analyzer System*, 2014).

Figure 3

*TEG Diagram in Relation to Clot Formation*
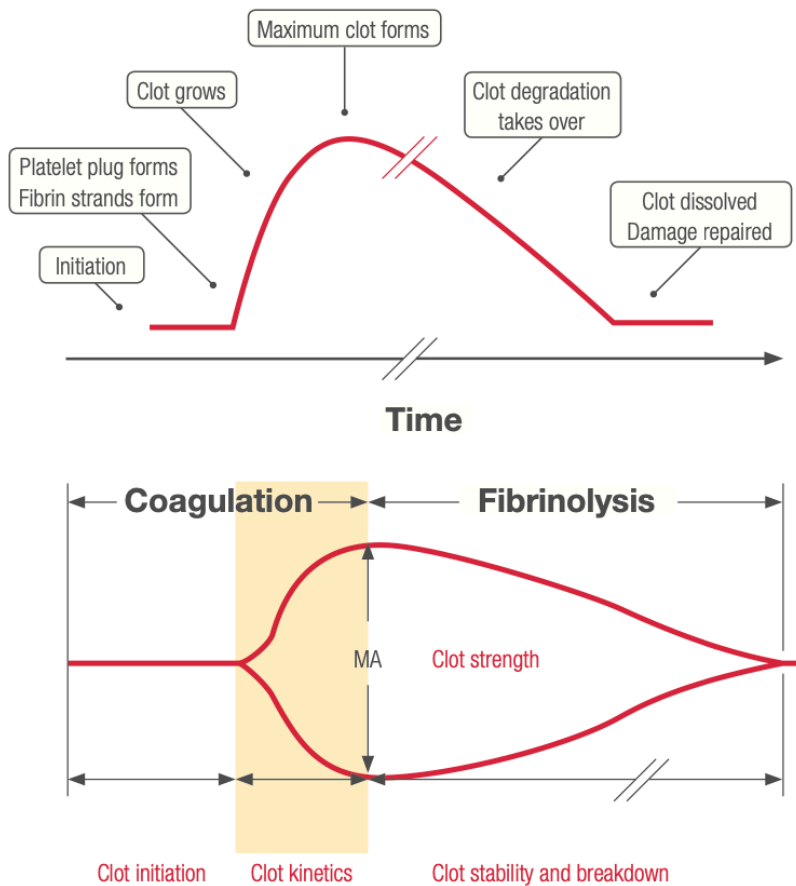
Note: This figure was produced by the Haemonetics corporation in 2014 for an informational pamphlet marketing the TEG5000 system. (*TEG 5000 hemostasis analyzer system.* (2014). Haemonetics Corporation. https://hospital.haemonetics.com/ /media/files/hospital/teg/col-pp-000078-ie_teg5000_brochure,-d-,pdf.pdf)

The diagram formed by a TEG tracing is generally divided into five parts for analysis. The R-time, K-time, alpha-angle, maximum amplitude (MA), and lysis at 30 minutes following the MA (LY 30). R and K times, as well as alpha angle are a measurement of clot formation (coagulation). The MA and LY30 are a measurement of clot breakdown (fibrinolysis). The R time is the time it takes to begin forming a clot and is representative of coagulation factor

function/the intrinsic pathway. A normal R-time value would be 5-10 minutes (Semon &

Cheatham, 2014). The K-time is the time in minutes until the clot achieves a fixed strength

(20mm on the Y-axis). This is an assessment of fibrinogen cross-linkage function and normally

takes 1-3 minutes (Semon & Cheatham, 2014). The alpha-angle is the angle/slope between the

baseline R-time and K-time on the diagram. It is also an assessment of fibrinogen, however

rather than initial formation, it is the speed of fibrin accumulation. A normal range would be 53-

72 degrees (Semon & Cheatham, 2014). The MA is defined as the highest vertical amplitude on

the TEG diagram and is a measurement of clot strength and subsequent platelet function. A

normal value has been defined as 50-70 mm (Semon & Cheatham, 2014). Clot breakdown, or

fibrinolysis, is denoted as LY 30 (or A30)—clot lysis at 30 minutes following the MA. The LY

30 is depicted as a percentage, with a normal value being 0-3%. Figure 4 depicts a standard

annotated TEG tracing.

Figure 4

A TEG Tracing
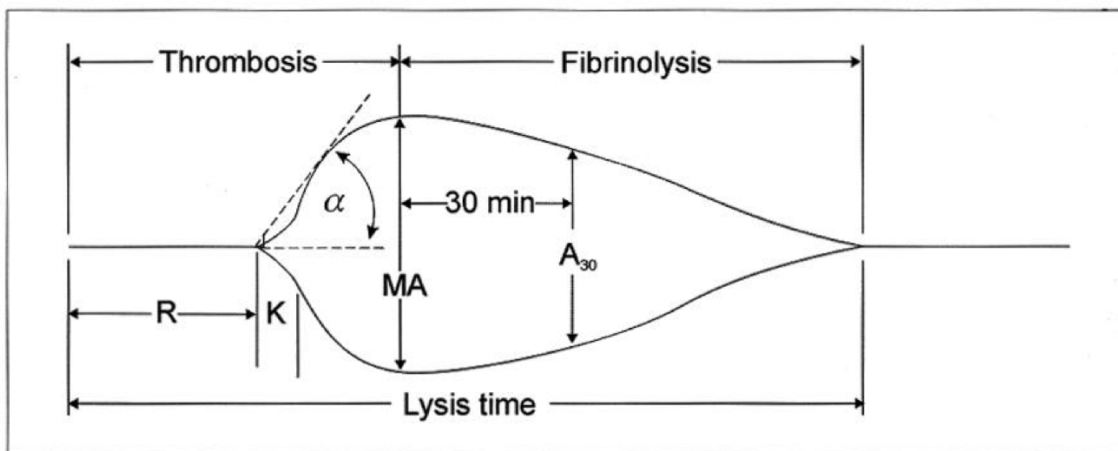
Note: This diagram is borrowed from the Orlando Regional Medical Center's Department of
Surgical Education TEG trauma guidelines (Semon & Cheatham, 2014).

A challenge regarding TEG interpretation is the variation in normal values. Currently,

the Haemonetics corporation has not responded to a request for defined normal and abnormal

values for TEG interpretation in the clinical setting. Therefore, one is left to assume that the

values utilized are organization specific. Variations currently exist within common anesthesia

educational sources, scholarly articles, and clinical resources (Brill et al, 2021; Sayce et al.,

2020; Semon & Cheatham, 2014; Shaydakov, 2022; *Thromboelastogram (TEG)*, 2023). The

limitations of this will be discussed later in this paper's literature review—as Baksaas-Aasen et

al. (2019) attempted to create a summary of values and protocols to guide TEG use and

management. However, an excellent and clear depiction of TEG values and their interpretation

was produced by the Orland Regional Medical Center's Department of Surgical Education (see

Figure 5).

Figure 5

TEG Normal Values and Interpretation

| TEG Value	Normal*	Description	Measures
TEG-ACT (rapid)	80 - 140 sec	"Activated clotting time" to initial fibrin formation	clotting factors (extrinsic/intrinsic pathways)
R time (conventional)	5.0 - 10.0 min	"Reaction time" to initial fibrin formation	clotting factors (intrinsic pathway)
K time	1.0 - 3.0 min	"Kinetic time" for fibrin cross linkage to reach 20 mm clot strength	fibrinogen, platelet number
α angle	53.0 - 72.0 degrees	Angle from baseline to slop of tracing that represents clot formation	fibrinogen, platelet number
MA	50.0 - 70.0 mm	Maximum amplitude of tracing	platelet number and function
G value	5.3 - 12.4 dynes/cm^2	Calculated value of clot strength	entire coagulation cascade
LY 30	0 - 3%	Clot lysis at 30 minutes following MA	fibrinolysis

Note: This diagram is borrowed from the Orlando Regional Medical Center's Department of Surgical Education TEG trauma guidelines (Semon & Cheatham, 2014).
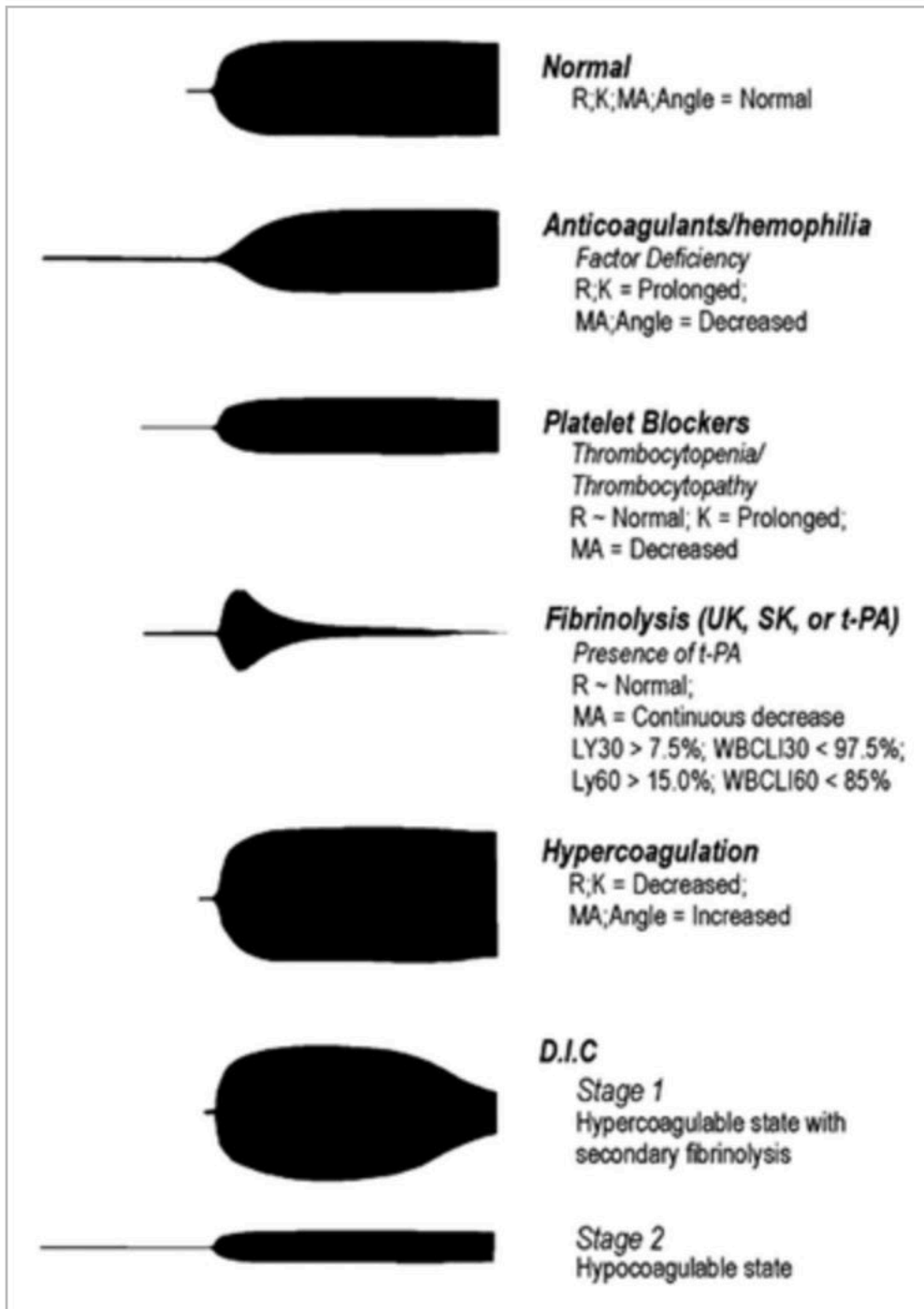
Abnormal TEG Results

   An abnormal TEG result is representative of coagulation dysfunction. The tracing will change depending on the affected aspect of coagulation. Figure 6 is a diagram produced by the Haemonetics corporation as a rough graphical depiction of different pathological processes and their corresponding TEG tracings. Physiologic states with poor coagulation and low levels of clotting factors, platelets, and fibrinogen have a narrower TEG tracing, while hypercoagulable states with high levels of clotting factors have a wide tracing.

Figure 6

Coagulation Pathologies and Their Corresponding TEG Tracing Shapes
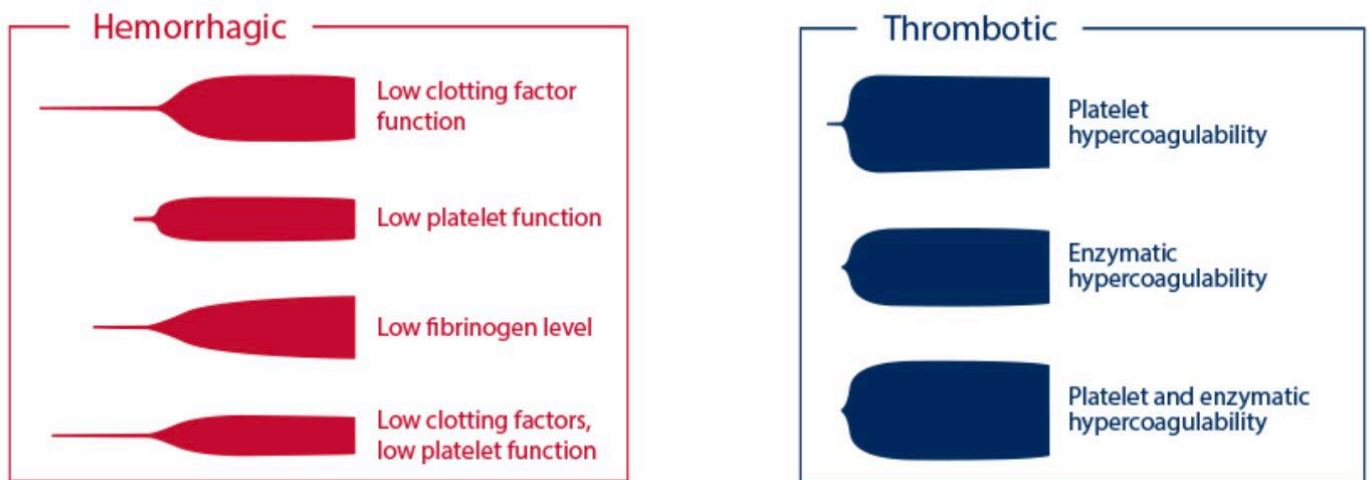
   In a 2014 article published in the American Journal of Hematology, Whiting and Dinardo provided a more detailed depiction of TEG tracings in various coagulopathic states and their corresponding values (see Figure 7) (Whiting & DiNardo, 2014).

Figure 7

Pathological TEG Tracings

Normal
R;K;MA;Angle = Normal

Anticoagulants/hemophilia
Factor Deficiency
R;K = Prolonged;
MA;Angle = Decreased

Platelet Blockers
Thrombocytopenia/
Thrombocytopathy
R ~ Normal; K = Prolonged;
MA = Decreased

Fibrinolysis (UK, SK, or t-PA)
Presence of t-PA
R ~ Normal;
MA = Continuous decrease
LY30 > 7.5%; WBCLI30 < 97.5%;
Ly60 > 15.0%; WBCLI60 < 85%

Hypercoagulation
R;K = Decreased;
MA;Angle = Increased

D.I.C
Stage 1
Hypercoagulable state with
secondary fibrinolysis

Stage 2
Hypocoagulable state

Note: Borrowed from Whiting, D., & DiNardo, J. A. (2014). TEG and ROTEM: Technology and clinical applications. *American Journal of Hematology*, *89*(2), 228-232. https://doi.org/10.1002/ajh.23599

TEG-Guided Transfusion

Guidelines regarding TEG and transfusion vary according to institution; however, they are all defined by a TEG value above a pre-determined normal range. Since different parts of the TEG tracing represent different aspects of the coagulation process, abnormalities in specific values determine which blood product should be administered. Figures 8 and 9 display excellent real-world examples of a hospital-wide policy of TEG-guided transfusion.
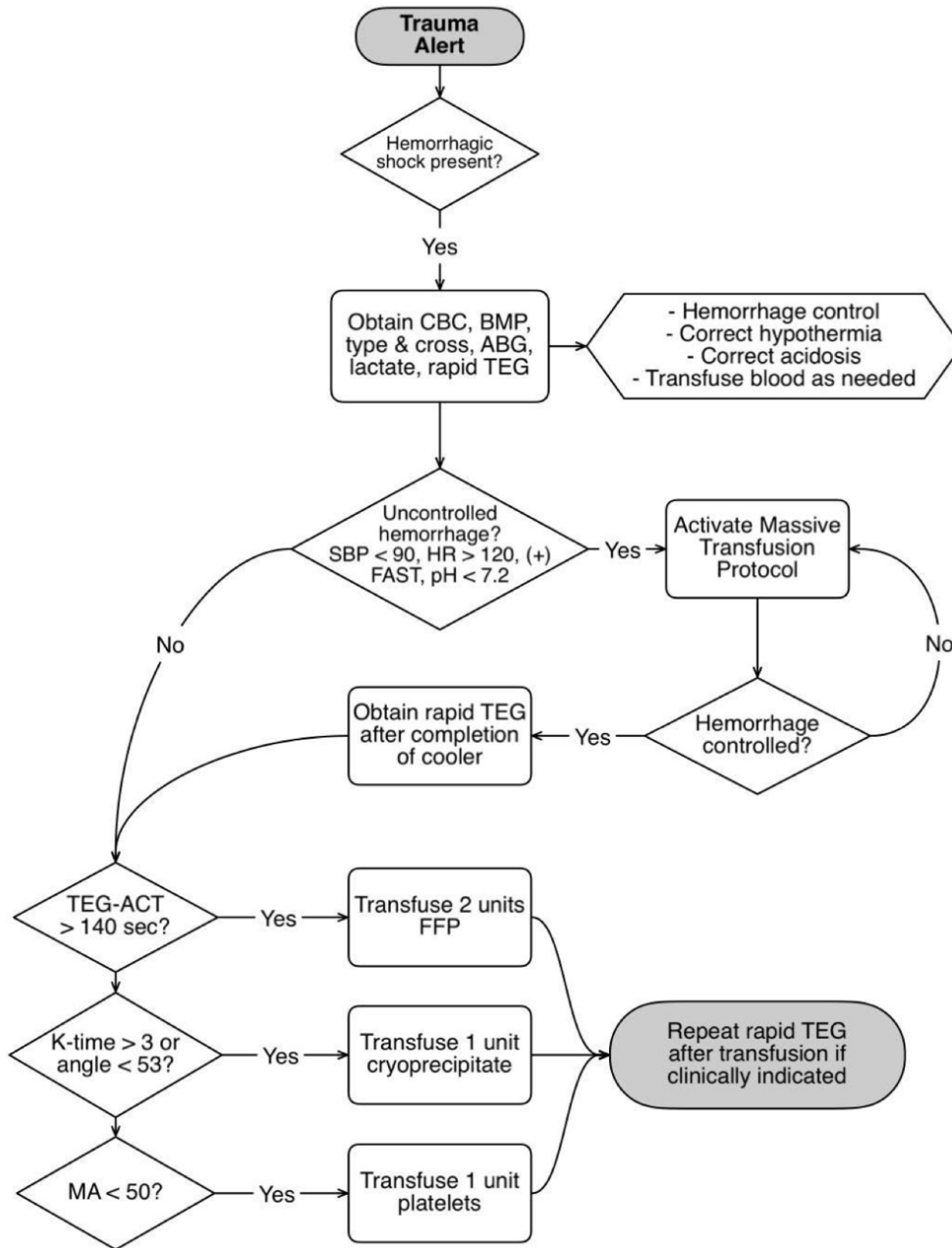
Figure 8

Abnormal TEG Value and Corresponding Blood Product for Transfusion

TEG Value	Transfuse
TEG-ACT > 140	FFP
R time > 10	FFP
K time > 3	cryoprecipitate
α angle < 53	cryoprecipitate +/- platelets
MA < 50	platelets
LY30 > 3%	tranexamic acid

Note: This diagram is borrowed from the Orlando Regional Medical Center's Department of Surgical Education TEG trauma guidelines (Semon & Cheatham, 2014).

Figure 9

Rapid Trauma Decision Tree Based Upon Abnormal TEG Values

Note: This diagram is borrowed from the Orlando Regional Medical Center's Department of Surgical Education TEG trauma guidelines (Semon & Cheatham, 2014).

Medical database 'UpToDate' also provides TEG-guided transfusion parameters (see

Figure 10). As mentioned previously, normal ranges and transfusion values vary between sources

(Brill et al., 2021; Sayce et al., 2020; Semon & Cheatham, 2014; Shaydakov, 2022;

Thromboelastogram (TEG), 2023).

Figure 10

UpToDate TEG-Guided Transfusion Parameters

r-TEG parameter	Normal range	Transfusion trigger
TEG-ACT	78-110 seconds	>128 seconds (FFP)
Alpha angle	66°-82°	<65° (cryoprecipitate)
MA (maximum amplitude)	54-72 mm	<54 mm (platelets)
LY-30 (lysis at 30 min)	0-7.5%	>5% (tranexamic acid)

Note: This graphic is featured in an article providing information and guidelines for the
management of coagulopathy in trauma patients (*Coagulopathy in Trauma Patients*, 2021).

An analysis of the history and contemporary clinical guidelines associated with TEG's

use in transfusion displayed by a deficit in standardized clinical guidelines for transfusion and

limited historical data regarding TEG's utility in the acutely coagulopathic trauma patient.

Subsequently, a literature review and analysis was performed.

Literature Review

Methods

A literature search was performed through the academic medical search engine PubMed.

Keywords utilized all in one group were "TEG, trauma, coagulopathy, protocol, resuscitation,

transfusion, thromboelastography". Exclusion criteria selected were the following: study

subjects less than 19 years-of-age, non-human animals, non-full-text, and non-English-language.

A search with only the key words "thromboelastograph" and "TEG" returned 1,930 results

between the dates of 1960-2022. When all key words were entered into the search tool, and

exclusions were utilized, 765 results were returned, with 279 published in the last five years. A filter of publication date within the past decade resulted in seven full-text articles. One of these results was a clinical trial, while six were retrospective reviews. When a filter of five years of publication date was applied, two full-text articles resulted. Of note, when the search term "protocol" was removed from the keywords entered and all other filters were left on, 25 results populated from the past 10 years, and 15 results populated from the past five years.

A review of the Haemonetics website was also conducted. Haemonetics is a global company and the manufacturer of the TEG system. They have registered trademarks of "TEG" "thromboelastograph" "rapidTEG" "TEG 5000" "TEG 6s" and "TEG manager" in the United States and other countries around the world. The website provided a description of the various TEG products, and links to company-selected peer-reviewed studies supporting their efficacy. All but two of the studies were over 10 years old and some of the authors have conflict-of-interest disclosures as consultants for the Haemonetics corporation. Videos regarding the TEG products were also provided on the website; however the links were non-functional. No data sheets or instructional materials describing TEG were provided on the website (TEG System: Haemonetics®, https://hospital.haemonetics.com/hemostasis-management).

A search using the medical reference site UpToDate was also performed. The search term "thromboelastography" resulted in no specific articles, however the site directed the user to a paragraph termed "Viscoelastic Testing" in an article titled "Platelet Function Testing" (Harrison & Lowe, 2022). Users were also directed to the "Thromboelastography" sub-section of an article titled "Coagulopathy in Trauma Patients" (Kutcher & Cohen, 2021), and a small entry in the "Point of Care" testing section of an article describing the clinical uses of laboratory coagulation tests (Zehnder, 2022).

Additionally, a Google Scholar search of "TEG", "trauma", "coagulopathy", "protocol", "resuscitation", "transfusion", and "thromboelastography" resulted in 2,180 items, with 1,290 published in the last five years. A review of current clinical trials as reported through the National Institute of Health with the keywords "TEG", "thromboelastography", and "thromboelastogram" resulted in 55 active adult studies in either recruitment or non-recruitment status. Active trials included TEG in specific diseases, extracorporeal membrane oxygenation (ECMO), and liver failure. At the time of search, there were no clinical trials in progress applicable to this paper's specific topic (ClinicalTrials.gov, n.d.).

Trauma-Induced Coagulopathy (TIC)

An analysis of the utility of thromboelastography in the acutely ill coagulopathic trauma patient requires an examination of the literature regarding the phenomenon of trauma induced coagulopathy (TIC). Also known as acute traumatic coagulopathy (ATC), acute coagulopathy of trauma shock (ACoTS), or post-traumatic coagulopathy (PTC) (Madurska et al., 2017), the syndrome is defined by impaired hemostasis and premature activation of fibrinolysis early in the post-injury period (Davenport et al., 2011; Kutcher & Cohen, 2021). Mechanisms of this phenomenon are poorly understood, however it appears to be a result of a combination of deficiencies in thrombin production, low or disordered fibrinogen, decreased platelet function, and either excessive or minimal fibrinolysis (Davenport et al., 2011; Kutcher & Cohen, 2021; Stettler et al., 2021). A review of literature published before 2017 revealed that tissue damage combined with systemic hypoperfusion appear to play a role (Brohi et al., 2003; Frith et al., 2010; Meledeo et al., 2017). It is also unclear if TIC is an early element of disseminated intravascular coagulation (DIC), or a separate physiological phenomenon. This concern is addressed in the most current version of the article *Coagulopathy in Trauma Patients* on the

medical information and guidance site UpToDate which concludes that TIC is mechanistically

distinct from DIC but that the two frequently overlap and more research is needed (Kutcher &

Cohen, 2021).

There is no formal definition of TIC. In a recent prospective observational multi-center

cohort study, Baksaas-Aasen et al. (2019) noted the lack of an accepted laboratory definition of

hyperfibrinolysis. The authors created their own guidelines based on existing literature and

defined TIC as an international normalized ratio (INR) >1.2, hyperfibrinogenemia as a

fibrinogen concentration >2.0g/L, and thrombocytopenia as a platelet count below $100x10^9$/L

(Baksaas-Aasen et al., 2019). These classifications are important as this paper formed the basis

of the later publication of the only randomized controlled trial of viscoelastic monitoring

compared to conventional coagulation tests in the trauma patient (Baksaas-Aasen et al., 2020).

Historically, risk and incidence of thrombosis and coagulopathies have been defined

through the lens of Virchows triad of venous stasis, vascular injury, and hypercoagulabilty

(Barash et al., 2013). Anesthesia textbooks as well as most contemporary medical publications

define additional mediators of coagulopathy as acidosis and hypothermia (Barash et al., 2013;

Brohi et al., 2003; Frith et al., 2010). Current literature also describes proposed mediators of

TIC as acidosis, hypothermia, and cellular/vascular modulators (Baksaas-Aasen et al., 2019;

Barash et al., 2013, Brohi et al., 2003; Frith et al., 2010; Sayce et al., 2020). In a systematic

search of peer-reviewed literature and product manuals regarding the role of TEG in trauma

resuscitation, Brill et al. (2021) provided one of the most extensive descriptions of TIC

modulators. The authors argued that thrombomodulin, the protein-C system, plasminogen

activator-inhibitor-1 (PAH-1), qualitative platelet dysfunction, and thrombogenic microparticle

release all constituted components of TIC (Brill et al, 2021).

In a retrospective data analysis of immediate clotting screen samples from emergency department (ED) patients admitted to a major trauma center, Brohi et al. (2003) found that 1/4 of patients arriving to the hospital were coagulopathic with a PT over 18 seconds or APTT over 60 seconds. Coagulopathies were associated with higher rates of complications such as greater transfusion requirements, longer intensive care unit (ICU) stays, and increased mortality (Brohi et al., 2003). This correlation between coagulopathies and increased mortality rates is well established in both historic and contemporary literature. Brohi et al. (2003) wrote of a four-fold increase in mortality rates in the trauma patient diagnosed with coagulopathy according to the previously mentioned parameters, and in a retrospective analysis of 17,200 data sets Maegele et al. (2007) described a 50% mortality rate in the acutely coagulopathic trauma patient. This data was recently corroborated by Brill et al. (2021).

Trauma and Transfusion

Contemporary trauma management is guided by estimates of the amount of current and expected blood loss, point-of-care (POC) laboratory tests, and institution-specific guidelines (Graetz & Nuttall, 2021). Succinctly summarizing the past 20 years of research, Baksaas-Aasen et al. (2020) wrote that contemporary approaches to trauma resuscitation place a focus on control of bleeding and management of TIC. The administration of hemostatic therapy is usually delivered as part of a MTP which provides tranexamic acid and blood components in proportions intended to replicate the composition of whole blood. The authors went on to summarize the conclusions in much of the contemporary scientific literature that these strategies were rarely able to fully correct coagulopathy once it was established, and that all patients tended to receive the same management approach regardless of the severity of the hemostatic dysfunction present (Baksaas-Aasen et al., 2020).

In a 2022 review of the literature on massive transfusion protocols and urgent blood administration, the United States' National Institute of Health defined massive transfusion as administration of greater than 10 units of packed red blood cells (PRBCs) within a 24-hour period (Jennings & Watson, 2022). Commonly accepted blood tests guiding such protocols are known as conventional coagulation tests (CCTs). Standard measurements utilized are prothrombin time (PT), international normalized ratio (INR), active partial thromboplastin time (aPTT), platelet count, and fibrinogen (Brill et al., 2021; Baksaas-Aasen et al., 2020, Graetz & Nuttall, 2021). While variations in normal values exist amount institutions, the most important conclusion from this review is that the turn-around time for CCTs is often significant. A prospective multicenter study of blood samples from patients undergoing major surgery in three different centers found the median turnaround time was 88 minutes for a lab-processed PT, with a range of 29-235 minutes (Toulon et al., 2009). Brill et al. (2021) discussed that the median time to death from hemorrhage is within three hours of injury, stating that the detection of TIC depends on rapid/point of care testing.

Viscoelastic Testing and Past Literature

The majority of literature regarding thromboelastography in management of the acutely bleeding adult trauma patient was published prior to 2017. Therefore, an analysis of the literature will be divided between historical (prior to 2017) and contemporary, within the last five years (2017 and later).

Historical Level-One Evidence

There is little historical level 1 evidence concerning TEG's use in place of CCTs in trauma resuscitation. An exception was a 2016 randomized-controlled trial published in the Annals of Surgery Journal (Gonzalez et al., 2016) with the hypothesis that a MTP guided by

assays such as TEG would improve survival rates compared to CCTs.   Subjects were injured

patients (n = 111) from an academic level 1 trauma center who met criteria for MTP activation.

Patients were randomized to be managed in the acute traumatic period by goal-directed TEG or

CCTs. The primary outcome was 28-day survival rates, and the authors found that utilization of

a goal-directed, TEG-guided MTP improved survival rates compared to CCT. In fact, Gonzalez

et al. (2016) found that TEG survival rates were significantly higher than the CCT group (log-

rank p = 0.032; Wilcoxian p = 0.027). While both groups required the same amount of PRBCs,

the CCT group required more plasma, [CCA: 2.0 units (0-4), TEG: 0.0 units (0-3), p = 0.022]

and platelets [Conventional Coagulation Assay: 0.0 units (0-1), TEG: 0.0 units (0-0), p = 0.04]

within the first two hours of resuscitation. This was the only randomized controlled study

published up to that point, and it showed that TEG-guided MTPs had not only had improved

survival rates, but patients required less blood products overall (Gonzalez et al., 2016).

Interestingly, the only other level 1 evidence from prior to five years ago directly

contradicted this result. Hunt et al. (2015) performed a narrative review of all cross-sectional

studies investigating the diagnostic accuracy of TEG in adult patients with clinically suspected

TIC/case-control studies in both civilian and military settings. The authors found no evidence

supporting the accuracy of TEG, or any other viscoelastic testing modalities (Hunt et al., 2015).

Additionally, Hunt et. al (2015) expressed concern regarding the lack of data for analysis. In

conclusion, the authors argued that, while the use of PT and INR were not optimal for TIC

diagnosis in the adult patient, they should be utilized due to the lack of current clinical consensus

(Hunt et al., 2015). The authors stated they were unable to offer guidance regarding TEG in

trauma due to it limited evidence, however that it may be useful for research purposes (Hunt et

al., 2015).

While the official publication date of the Cochrane review was 2015 and the publication date of the RCT was 2016, the period is still close together. Neither study makes mention of the other. However, the fact that the Cochrane review mentioned a lack of applicable studies and no randomized controlled trials in contemporary literature is quite germane to the chronologically subsequent publication of Gonzalez et al. (2016).

Historical Level Two and Three Evidence

While there is limited Level 1 evidence concerning the superiority of TEG in the treatment of TIC in the period greater than five years ago, there are a reasonable number of articles that are level II and III evidence concerning the topic. The majority of studies are retrospective analyses based on data extraction from trauma centers.

A particularly robust example of this is a 2014 analysis conducted by Da Luz et al. The authors' descriptive systematic review ($N = 12,489$ participants) of observational studies: prospective cohort studies ($n = 38$), retrospective cohort studies ($n = 15$), and before-after studies ($n = 2$) showed limited evidence from observational data to suggest that viscoelastic testing may be effective in the diagnosis of early trauma coagulopathy or that abnormal TEG values may be predictive of blood-product transfusion/mortality in trauma settings (Da Luz et al., 2014). The analysis focused on viscoelastic testing's role in the diagnosis of early trauma coagulopathies with the outcomes of hypercoagulability, hypocoagulability, platelet dysfunction, and hyperfibrinolysis (Da Luz et al., 2014). Extensive data analysis was performed on the studies individually and collectively utilizing the Newcastle-Ottawa scale (NOS) for observational studies, and the QUADAS-2 tool for diagnostic accuracy studies.

Concerning the utility of viscoelastic testing in the diagnosis and correction of TIC, the authors concluded that viscoelastic testing may be superior to CCTs in the diagnosis and

prevention of acute traumatic coagulopathies (Da Luz et. al, 2014). However, Da Luz et al. (2014) concluded that while TEG and ROETM abnormalities may be predictive of the need for massive transfusion as well as mortality rates, their performance is not superior to CCTs (Da Luz et al., 2014). In assessing the previous literature, the authors also frequently noted the absence of randomized trials concerning viscoelastic testing in this field.

Historical Lower Levels of Evidence

Works with lower levels of evidence prior to 2017 tended to take the form of literature research review articles (Geeraedts et al., 2009; Hess et al., 2008; Sakran et al., 2012). While the majority focus on a discussion of TIC--its etiology, complexity, and treatment, Geeraedts et al. (2009) provided an excellent description of guidelines and evidence utilized for pre-2017 trauma resuscitation practices. In a literature review incorporating contemporary clinical guidelines and studies, the authors argued that TEG testing within the first 10 minutes of hospital admission can help guide blood product administration (Geeraedts et al., 2009). Echoing the concerns regarding time and clot dynamic issues discussed earlier in this manuscript, the authors concluded that CCTs may not reflect actual coagulation status in the patient, are time consuming, and do not appropriately represent coagulation function (Geeraedts et al., 2009). Geeraedts et al. (2009) argued that TEG does have clinical potential based on the previous works by Kaufmann et al. (2017) and that TEG as a point-of-care test for coagulation status in massive blood loss can provide information about actual clot formation and stability shortly (10 minutes) after the blood sample is obtained. Subsequently, coagulopathy due to hyperfibrinolysis or decreased platelet function/ numbers can be rapidly detected and countered.

Contemporary Level-One Evidence

The 2020 Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy (ITACTIC) trial, conducted by Baksaas-Aasen et al. is the only multi-center randomized controlled trial comparing viscoelastic testing directly to CCTs in the past five years. Researchers collected data from trauma patients at seven major European centers who qualified for massive hemorrhage protocol ($n = 396$) and received either viscoelastic hemostatic assays (VHAs) or CCT-guided interventions. The term viscoelastic hemostatic assays was used to refer to real-time tests of coagulation function, and included TEG and another test primarily utilized in Europe known as Rotational Thromboelastography (ROTEM). Primary outcomes were that the patient remained alive and free of massive transfusion (10 or more red cell transfusions) after 24 hours and secondary outcomes were 28-day mortality (Baksaas-Aasen et al., 2020). At 24 hours, there was no difference in the proportion of patients who were alive and free of massive transfusion (VHA: 67%, CCT 64%). Baksaas-Aasen et al. (2020) also found that 28-day mortality was not different overall (VHA: 25%, CCT 28%, *OR* 0.84, 95% *CI* 0.54-1.31) and there were no differences in additional secondary outcomes or serious events (Baksaas-Aasen et al., 2020). The authors concluded "when standard of care is delivered with empiric balanced haemostatic therapy and intensive conventional coagulation testing, viscoelastic haemostatic assays did not improve clinical outcomes in the intention to treat cohort" (Baksaas-Aasen et al., 2020, p. 50).

This conclusion echoes that of the 2015 Cochrane review. However, an interesting finding was that 67% of the patients being managed with viscoelastic testing received interventions related to coagulation deficits. These interventions took to form of PRBCs, or a 1:1:1 ratio of RBCs, plasma, and platelets. This was 1.8 times more interventions than the patient group being managed by CCTs. The authors argued this indicated a widespread

occurrence of coagulation deficits that were not detected by CCTs (Baksaas-Aasen et al., 2020).

Baksaas-Aasen et al. (2020) asserted that, with bleeding trauma patients, when standard care was

delivered in combination with empiric balanced transfusion therapy and intensive CCT

monitoring, VHAs identified more coagulation deficits. However, it is important to note that the

identification of coagulation deficits and subsequent delivery of interventions did not make a

difference in outcomes in this study (Baksaas-Aasen et al., 2020).

Additional high-level evidence to support viscoelastic testing's potential to identify

coagulation abnormalities was published in the European Journal of Trauma and Emergency

Surgery (Spasiano et al., 2020). In a single-center prospective observational cohort study of

severe trauma patients transported by helicopter evacuation crews, the authors found widespread

coagulation abnormalities to be present immediately after trauma in the pre-hospital setting.

This was evident in the shortening of the TEG R parameter and the prominence of the TEG

hypercoagulation profile (Spasiano et al., 2020).

The results of the ITACTIC trial showed no difference in clinical outcomes, however the

study provided significant data for further research. An example of this was a post-hoc analysis

of the ITACTIC trial to determine if rapid TEG results corresponded with traditional TEG values

(Vigstedt et al., 2022). In a post-hoc analysis of the ITACTIC RCT, Vigstedt et al. (2022)

examined available ($n = 187$) data from newly developed, POC cartridge-based TEG6s systems

and analyzed it against subsequent patient data of traditional laboratory run TEG 5000 maximum

amplitudes (MA). Researchers found that TEG-6s early amplitudes were sensitive (96-100%)

and specific (92-99%) predictors of low TEG tracing MA in severely injured trauma patients

displaying signs of hemorrhagic shock (Vigstedt et al., 2022). Based on these data, the authors

concluded that intervening on early amplitudes may minimize delays in hemostatic resuscitation

(Vigstedt et al., 2022).

Contemporary Level Two and Three Evidence

Prior to the ITACTIC study, Baksaas-Aasen et al. conducted a study with the goal of

developing ROETM and TEG algorithms for the hemorrhaging trauma patient (Baksaas-Aasen

et al., 2019). This large *(N* = 2,287) prospective observational multi-center cohort study was part

of the Targeted Action for Curing Trauma Induced Coagulopathy (TACTIC) trials. This

TACTIC trial is part of a larger body of work by the International Trauma Research Network

(INTRN). In this five-year study, patients were recruited from the same six major European

trauma centers used in the ITACTIC study. An analysis of patient admission data from CCTs,

ROTEM, and TEG were done via univariate regression models with the intention of developing

threshold parameters for the identification of TIC across testing modalities (Baksaas-Aasen et al.,

2019). These are summarized below in Figure 11.

Figure 11

Baksaas-Aasen et al.'s Constructed Coagulopathy Management Guidelines
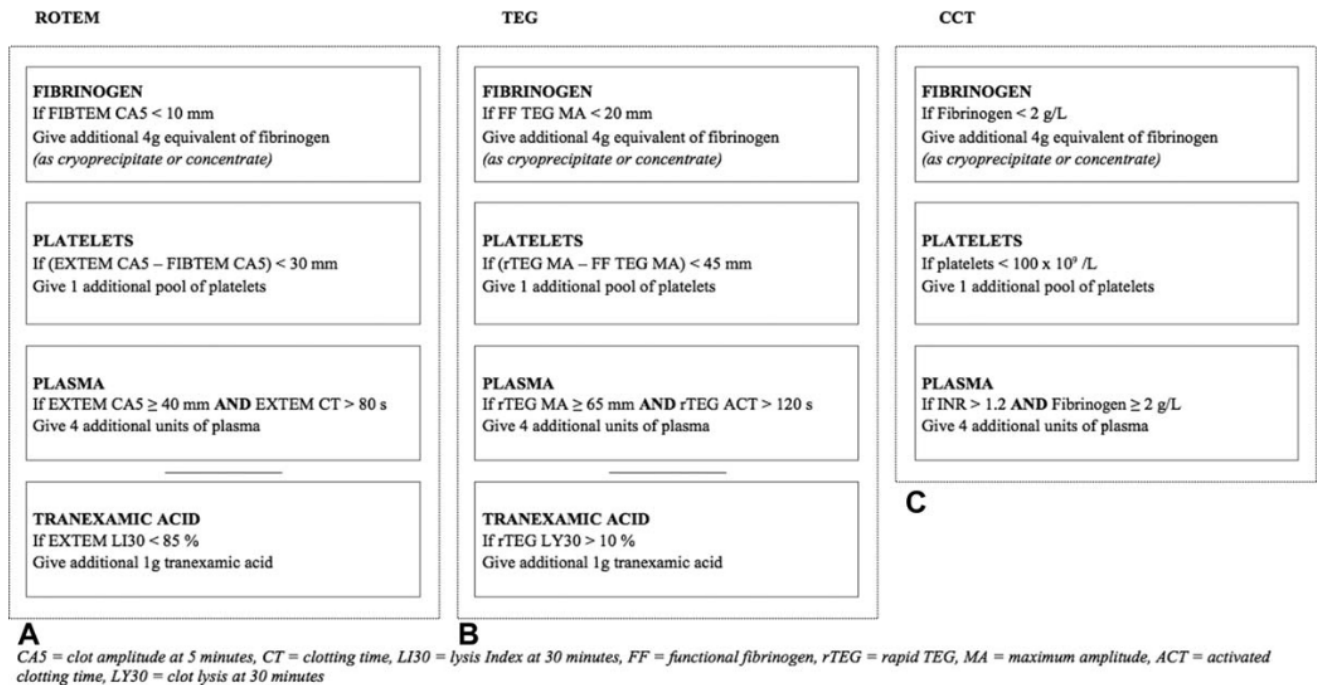
Note: This figure was produced by Baksaas-Aasen et al. in 2019 as a summary of laboratory values and subsequent protocols to be used in addition to damage control resuscitation in the management of TIC during trauma hemorrhage. From "Data-driven development of ROTEM and TEG algorithms for the management of trauma hemorrhage" by Baksaas-Aasen et al., 2019, *Annals of Surgery*, *270*(6), 1178-1185. https://doi.org/10.1097/sla.0000000000002825

The guidelines depicted in Figure 11 were slightly different than those proposed in a 2017 receiver operating characteristic (ROC) analysis by Einerson et. al., (2017). However, that study had only 190 participants in contrast to 2,287 in the TACTIC study (Baksaas-Aasen et al., 2019). The authors also advocated for a prospective multicenter study, which Baksaas-Aasen et al. subsequently conducted (2019, 2020).

Additional level two and three studies in the contemporary period have focused on understanding the limitations of currently laboratory measurements of TIC and how to best correct coagulopathy associated with it. Drawing data from the ITACTIC and TACTIC trials, a

2022 retrospective analysis (*n*= 211) by Moore et al. (2022) assessed TIC from the level of

proteomics. SomaLogic proteomic analysis of 1,305 proteins were performed. The authors

concluded that the current laboratory and clinical assessment may not capture the large number

of proteins involved and there are opportunities to identify patients at risk for massive bleeding

and transfusion (Moore et al., 2022). Additionally, in a 2017 prospective multi-center

observational study, Balvers et. al (2017) found that a high platelet/plasma to RBC transfusion

ratio combined with TXA use was associated with decreased need for massive transfusion and

increased survival. However, no strategies were associated with correction of coagulopathy

(Balvers et al., 2017). In a systematic search of peer-reviewed literature and product manuals,

Brill et. al (2021) argued that viscoelastic testing could predict massive transfusion requirements

and identify trauma-induced coagulopathy better than clinical judgement or CCTs. However,

this was directly contradicted by the ITACTIC trial---even if viscoelastic testing was a better

predictor of coagulopathy, under the current treatment algorithm the clinical outcomes are

unchanged (Baksaas-Aasen et al., 2020; Brill et al., 2021).

Contemporary Lower Levels of Evidence

There are multiple lower-level reviews and guidelines regarding the use of viscoelastic

testing in ATC, however they still suffer from the lack of RCTs on the subject. In a review

article incorporating contemporary clinical guidelines, Gonzalez et al. (2017) argued that

viscoelastic assays are a better representation of TIC than CCAs, and TEG has use in the real-

time guidance of massive transfusion protocol as well as provide insights into TIC (Gonzalez et

al., 2017). The authors did an excellent job of explaining the history, interpretation, and

methodology of TEG analysis, however, this review is limited by a lack of direct experimental

data. Similarly, in a 2017 research agenda for trauma critical care, Asehnoune et al. (2017)

provided a comprehensive description of the complexities of trauma resuscitation while advocating for further RCTs specifically regarding the role of viscoelastic monitoring and coagulation therapeutics in trauma resuscitation.

Discussion

Literature Limitations

The greatest limitation regarding the utility of viscoelastic testing in the acutely coagulopathic adult trauma patient is the lack of level-1 evidence—specifically experimental and randomized controlled trials. Gonzalez et al. conducted a small RCT in 2016, and concluded that goal-directed, TEG-guided massive transfusion in the acutely injured patient resulted in improved survival rates compared to CCT-guided TEG. They also found that a TEG-guided MTP resulted in less plasma and platelet transfusion during the early phase of resuscitation (Gonzalez, et. al., 2016). However, the much larger 2015 Cochrane review showed different results (Hunt et al., 2015). The only level 1 evidence published in the past five years concerning TEG's use in the coagulopathic trauma patient is Baksaas-Aasen et al.'s 2020 ITACTIC trial in which the conclusions echoed that of the earlier Cochrane review.

A potential area of additional research addressed in many of the studies is TEG's utility in diagnosing coagulopathy faster and more comprehensively than CCTs. Da Luz et al.'s (2014) work is an excellent example of this. Toulon et al. (2009) also provide context for the long turn-around-time of CCTs in diagnosis and treatment of ATC. These conclusions were echoed by Brill et al. (2021) in their description of both the limitations of CCTs and examination of the TEGs graphical representation of active coagulopathies.

Clinical Limitations

Clinically, TEG suffers from certain limitations. Intrinsic to the technology is that it requires a multi-step coordinated process between hospital departments and services. The drawing of the blood sample, processing, and interpretation of the data often involve extensive communication. A system-wide digital platform is also necessary to follow the patient from the trauma bay to the operating room (OR) while allowing real-time coagulation data to be readily available. Because TEG is intended to be a rapid POC analysis, all these systems must function efficiently at all hours. This issue could potentially be mitigated by the utilization of cartridge based POC systems such as the newer TEG 6s.

One of the more appealing aspects of TEG is the visual simplicity of the tracing. However, interpretation of the TEG waveform may initially be challenging. While many clinicians are familiar with CCTs, not as many are comfortable with the use of TEG and its interpretation (Sayce et al., 2020). Consequently, provider education and materials for rapid analysis and decision-making aids must be combined with TEG utilization. (Semon & Cheatham, 2014).   Additionally, there is no current standardization of lab parameters for TEG analysis in trauma treatment and management. Sayce et al., (2020) noted that the transfusion triggers for TEG are often based on clinician judgement rather than data-driven guidelines.

Future Directions

The conflicting evidence regarding TEG's use in acute traumatic coagulopathy may be an argument for TEG's use in conjunction with CCTs (Brill et al., 2021; Toulon et al., 2009). Since the turnaround time of a standard CCT is significantly longer than TEG (Toulon et al., 2009), a good option for optimizing outcomes would be TEG and CCTs both drawn and analyzed on admission for every trauma patient. The TEG would then be repeated every 15 minutes to assess

ongoing coagulopathies and guide therapy in conjunction with the clinical information provided by CCT's.

A future direction of research is contemporary science's lack of information regarding TICs and the coagulation process in general. Multiple studies have discussed the intrinsic limiting factor of studying TIC as a part of a generalized human coagulation process that is not fully understood (Barash et al., 2013; Meledo et al., 2017; Moore et al., 2022). To make matters more complicated, there is no consensus on lab values that define TIC, so researchers are left to decide which values they prefer to utilize for each individual study (Baksaas-Aasen et al., 2019).

A significant area of future research may also be the proteins and chemical cascades associated with TIC. An example of this is how Moore et al. (2022) utilized proteomics, to analyze a potential spectrum of dysregulated proteins that are not adequately measured in standard TIC lab tests.

Conclusion

Thromboelastography provides an elegant visual representation of multiple data points associated with the poorly understood syndrome of trauma induced coagulopathy. It provides a real-time analysis of the dynamic process of clot formation and breakdown, and it can be utilized to guide anesthesia interventions and transfusion therapies (Baksaas-Aasen et al., 2019; Sayce et al., 2020).

The utility of TEG in the anesthetic management and acute perioperative trauma resuscitation of the adult coagulopathic patient suffers from a deficit of level-1 evidence (Baksaas-Aasen et al., 2019; Hunt et al., 2015), a lack of standardized lab values, and potential issues with streamlining institutional processes and clinician education. However, TEG may be effective in diagnosing TIC more rapidly than conventional coagulation tests, differentiating

injury-related fibrinolysis phenotypes, and reducing use of blood products while simultaneously guiding therapies (Baksaas-Aasen et al., 2020; Brill et al., 2021; Sayce et al., 2020).

When forced to solely rely on clinical gestalt, Brill et al., wrote "even experienced clinicians predict poorly the need for massive transfusion based on judgement alone" (2021, p. 54). In the analysis of the acutely coagulopathic patient, TEG provides a global ongoing assessment of clotting and in conjunction with the static data derived from CCTs can serve as an important source of information to the anesthesia provider and from which effective clinical decisions can be made.

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