Why is everyone so excited about thromboelastrography (TEG)?
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Abstract
Thromboelastography (TEG) is one of the most common whole-blood viscoelastic coagulation tests used in clinical laboratories and at the point of care. TEG provides information on coagulation defects that are often difficult to detect using routine laboratory tests such as activated partial prothrombin time or prothrombin time. In certain critically ill patient populations, the use of TEG instead of or in addition to routine laboratory coagulation tests has been shown to improve outcomes or reduce transfusion requirements. However, TEG and other viscoelastic coagulation tests are affected by unique pre-analytic and analytic variables that do not impact other common laboratory coagulation tests. In this review the underlying principles, clinical applications, and laboratory aspects of TEG testing are discussed.

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1. Introduction

Blood coagulation is a complex but essential biological process. Coagulation is sometimes categorized from an observational point of view into phases of hemostasis: first, a defect in the blood vessel (endothelial damage) occurs, which triggers the need for blood clotting to prevent excessive blood loss, then a platelet plug forms to temporarily slow blood loss (often called the “white clot”), followed by a series of biochemical reactions to generate thrombin in order to cleave fibrinogen into a network of fibrin to provide a stronger and more permanent repair (“red clot”), and finally clot lysis (fibrinolysis) to allow tissue remodeling and repair.

Biochemically, these same observations can be divided into subcomponents that are measured to predict the body’s ability to respond to vascular damage (stop bleeding). The activation of enzymes necessary to form fibrin are artificially divided into intrinsic (predominantly dependent upon coagulation factors VIII, IX, XI, and XII), extrinsic (predominantly dependent upon tissue factor and factor VII), and common (predominantly dependent upon factor Xa and thrombin activity and fibrinogen concentration) pathways for laboratory measurement. The availability of platelets (to initiate coagulation through platelet activation and to provide a surface for biochemical reactions in the common pathway) is commonly measured by obtaining platelet counts, although numerous other measures of platelet activity exist. To assess the coagulation status of critically ill patients, clinicians are most often left with a series of “snapshots” that involve assessment of the intrinsic (activated partial prothrombin time, aPTT), extrinsic (prothrombin time, PT), and common (thrombin time) pathways as well as platelet counts to estimate platelet activity available for hemostasis. D-dimer and related tests can assess for fibrinolysis (e.g., that observed during venous thrombosis), although these tests do not adequately differentiate acute vs. ongoing fibrinolysis.

These common laboratory coagulation tests most often provide all the information needed for clinicians to diagnose and treat disorders of hemostasis. However, critically ill patients often have coagulation disorders that are not adequately detected or described by conventional coagulation tests. Platelet count is not a good substitute for platelet function in patients treated with certain medications or after certain procedures that may impact platelet function. Few laboratory tests can...
detect and differentiate acute fibrinolysis that can occur during long surgical procedures, such as liver transplant, from ongoing fibrinolysis after thrombosis. The PT and aPTT laboratory tests are sensitive only to relatively large changes in clotting factor concentrations. Thus, they may lack sufficient sensitivity to detect coagulation changes in patients with massive trauma or other conditions in which early detection of clotting factor deficiency is key to preventing massive hemorrhage. Finally, plasma-based coagulation tests do not provide information on the cellular contribution to coagulation. For these reasons and others, interest in whole-blood viscoelastic coagulation testing has increased in recent years.

Viscoelastic coagulation testing has become a popular addition or alternative to conventional (aPTT, PT, thrombin time, platelet count, and D-dimer) coagulation tests in critical care. Unlike the conventional coagulation tests that take snapshots of isolated parts of the coagulation process, viscoelastic coagulation testing monitors the clotting of whole blood in a cup or small container. One of the most commonly used (but not the only) viscoelastic clotting test is thromboelastography (TEG), which will be the subject of the remainder of this review.

2. Thromboelastography (TEG)

TEG testing relies upon changes in the viscosity of blood as it coagulates, along with fibrin and platelet-dependent cross-linking between whole blood in a cup and an object (pin) inserted into that cup, to provide information on the sufficiency of hemostasis and detect coagulation defects. The TEG instrument (Fig. 1) consists of a plastic plate, upon which is placed a disposable cup, attached via mechanical arms to the TEG device. Whole blood is placed in the disposable cup, and after activation of clotting (usually with kaolin), the plastic plate and cup are moved up into contact with the pin. At this point, the TEG tracing is initiated. After the tracing is initiated, the mechanical arms on the TEG instrument rotate the cup at a fixed frequency. Initially the pin, attached to the instrument via a torsion wire, will be motionless in the cup of whole blood as there is no means for the liquid whole blood to exert force on the pin (Fig. 2). As whole blood begins to clot, the viscosity of the blood increases, and at the same time the pin becomes cross-linked to the cup via fibrin and platelet interactions. As the pin begins to move in concert with the cup, this motion is transduced (via the torsion wire) to produce the TEG tracing.

![Fig. 2. Schematic representation of the cup (of whole blood), pin, and torsion wire on the TEG® device. After initiation of clotting, the plate/cup apparatus is moved up such that the pin is immersed in whole blood. Initially, the liquid whole blood exerts no force on the pin/torsion wire. As blood clots, the viscosity of the blood increases, and the pin becomes cross-linked to the cup via fibrin and platelet interactions. As the pin begins to move in concert with the cup, this motion is transduced (via the torsion wire) to produce the TEG® tracing.](image-url)

in concert with the cup, this motion is transduced (via the torsion wire) to produce the TEG tracing (Fig. 3). The parameters of a TEG tracing include the reaction (R) time, the time from initiation of the TEG tracing until torsion is exerted on the pin/wire assembly, R time largely reflects the adequacy of coagulation factors (similar to what is measured in the laboratory by PT and aPTT). The K time (time to reach 20 mm clot amplitude) and the angle (formed by line tangent to clot curve, Fig. 3) reflect clot kinetics and are determined by a number of factors including thrombin generation and fibrinogen concentration. The maximum amplitude (MA) is the maximum distance traveled by the cross-linked cup/pin, which reflects maximum clot strength and is largely a function of platelet function or activity. Finally, the Lysis30 or Lysis60 is the percent decrease in area under the TEG curve (from MA) over 30 or 60 min.

All of these parameters can be compared to normal or reference values to detect either clotting factor deficiencies (increased R time), fibrinogen deficiencies (decreased angle), platelet function defects (decreased MA), or excess fibrinolysis (Lys30 or Lys60 outside of reference values). The TEG tracing thus provides an overview of multiple coagulation processes and allows detection of variables that impact conventional coagulation tests (such as clotting factor deficiencies), as well as factors that cannot be easily measured by conventional testing (clot kinetics which is dependent upon both thrombin generation and fibrinogen concentration, platelet function, and fibrinolysis). In Fig. 4, a TEG tracing with both prolonged R time (indicating factor deficiency and/or the presence of heparin) and reduced MA (indicating a platelet function defect) is demonstrated. This type of abnormal tracing might be expected from a patient with coagulopathy during cardiovascular surgery or massive transfusion. In Fig. 5, excess fibrinolysis in an otherwise normal TEG tracing is demonstrated.

Another advantage (or disadvantage, depending upon the clinical situation and application) of TEG over conventional coagulation testing is that the TEG R time is significantly more sensitive to clotting factor deficiencies or the presence of heparin than are conventional tests such as aPTT or PT. A special cup containing heparinase can be used to determine whether the presence of heparin (administered therapeutically or through accidental sample contamination) has influenced the TEG parameters.
3. Clinical applications of TEG

TEG was developed in the 1940s in Germany as a comprehensive measure of blood coagulation to facilitate research. Its use in clinical practice was not described until many years later (1960s) when physicians performing early liver transplantation surgeries described use of TEG to detect and treat fibrinolysis occurring after reperfusion of the transplanted liver [1]. As the clinical practice of liver transplantation matured in the 1980s, researchers at the University of Pittsburgh began to describe the use of TEG to detect and treat pre-existing coagulopathies due to liver failure in patients before transplantation, dilutional coagulopathies during liver transplant surgery, and fibrinolysis resulting from reperfusion of the transplanted liver [1]. Liver transplant represented the ideal application for a viscoelastic whole-blood coagulation test because conventional coagulation testing (e.g., aPTT or PT) was affected by the presence of heparin used during the surgery. In addition, fibrinogen concentration did not always reflect functional fibrinogen activity due to acquired dysfibrinogenemia, platelet count was not always reflective of platelet function, and tests such as D-dimer or fibrin degradation product were difficult to interpret in the context of a long and invasive surgery [1].

In a study of 66 consecutive liver transplant patients, Kang and colleagues demonstrated that correlation between conventional coagulation tests and TEG parameters was poor, and that a transfusion algorithm based upon TEG parameters (rather than conventional coagulation test results) resulted in less blood product usage compared to historical controls with transfusion guided by conventional coagulation testing. The era of the TEG-guided transfusion algorithm was born [1]. As enhanced fibrinolysis is one of the most striking coagulation defects occurring during liver transplantation [2,3], TEG has gained widespread use in liver transplantation because of its improved ability to detect fibrinolysis compared to conventional coagulation tests. One report also suggested that preoperative assessment of coagulation using TEG could predict development of intraoperative fibrinolysis during liver transplantation [3], although several other studies have failed to demonstrate a relationship between preoperative coagulation parameters and intraoperative transfusion requirements [4–6].

The description of TEG-based coagulation monitoring and TEG-guided transfusion algorithms during liver transplant increased interest in TEG for other invasive procedures that involved coagulopathy, most notably cardiovascular surgery. A randomized study published in 1999 compared blood product usage and bleeding during and after cardiovascular surgery in patients assigned to a transfusion algorithm guided by TEG R and MA (as well as laboratory platelet count and fibrinogen concentration), compared to a control group with transfusion need determined from activated clotting time, platelet count and prothrombin

Fig. 3. TEG® tracing. Reaction (R) time, angle, and maximum amplitude (MA) are demonstrated. K is the time (in minutes) required to reach 20 mm amplitude. Lys30 is the percent decrease in area under the TEG® curve (from MA) over 30 min, while Lys60 is the percent decrease over 60 min.

Fig. 4. TEG® tracing demonstrating prolonged reaction (R) time and reduced maximum amplitude (MA).
time [7]. The primary findings were that postoperative transfusion of fresh frozen plasma and platelet transfusions (as well as total FFP and platelet transfusions) were decreased in the group with TEG monitoring [7]. A large retrospective study also found that a TEG-guided transfusion algorithm during cardiac surgery significantly reduced both perioperative and total transfusion requirements [8].

Another prospective study used both conventional coagulation tests and TEG to determine which tests of coagulation could best identify cardiovascular surgery patients that went on (postoperatively) to have excessive blood loss. After receiver operator characteristic (ROC) curve analysis of each coagulation test to determine ability to predict postoperative blood loss, the authors proposed a cardiovascular surgery transfusion algorithm including both conventional (PT, aPTT, fibrinogen, and platelet count) and TEG (MA) parameters [9]. As observed in liver transplantation, TEG has been found valuable in cardiovascular surgery because it allows rapid identification of defects in clotting factor concentration, platelet function, and thrombin generation and/or fibrinogen concentration that are not always detectable by routine coagulation testing [7–9]. An additional advantage of TEG is the ability to detect coagulation abnormalities even in the presence of high levels of therapeutic heparin (by using the heparinase cup) encountered during cardiovascular surgery [10].

It should be noted, however, that successful cardiovascular surgery transfusion algorithms have been developed utilizing tests other than TEG [11,12]. In fact, one study found no difference in blood product transfusion when patients were randomized into one group where point of care testing (including TEG) was used to make transfusion decisions and another that used conventional laboratory coagulation tests to guide transfusions [12]. It remains unclear how much the success of any particular cardiovascular surgery transfusion algorithm is dependent upon the particular coagulation tests employed to detect coagulopathy and how much is a function of the existence of a transfusion algorithm to encourage conservative use of blood products.

Trauma is another critical care application for TEG. Approximately 25%–35% of trauma patients present with coagulopathy, which is associated with increased morbidity and mortality [13]. Conventional laboratory coagulation tests do not always detect coagulopathies that exist when patients with severe trauma initially present for evaluation [13]. One study showed that among patients with penetrating injuries, TEG MA obtained in the first 6 h after admission correlated better with subsequent blood product usage than conventional coagulation tests obtained at admission [14]. Another study found that TEG parameters could detect coagulopathy, platelet dysfunction and hyperfibrinolysis early during trauma resuscitation, and that development of these coagulation disorders was associated with mortality [15]. Based upon these and other observations [16,17], interest in TEG for severe (especially penetrating) trauma has increased substantially in recent years.

Recently, a systematic review of the benefits and harms of using TEG-guided transfusion strategies among patients with severe bleeding was conducted [18]. While the number of randomized studies found appropriate for inclusion was small (9 studies with a total of 776 participants), the systematic review did conclude that use of viscoelastic testing significantly reduced bleeding in patients with massive bleeding. Perhaps due to small number of studies (n = 5) that included a mortality endpoint, the review did not find a difference in mortality rate between conventional treatment and use of viscoelastic testing to guide transfusion therapy in this patient population [18].

4. Laboratory considerations for TEG Testing

TEG was designed for use with fresh whole-blood samples, but the use of fresh whole blood requires initiation of the TEG tracing within 4 min of sample collection (blood draw). For this reason, most TEG operators now use citrated samples for analysis [19]. However, both systematic differences and artifacts in TEG tracings have been described when comparing fresh whole blood to citrated blood samples. One study found that both R time and MA decreased over 30 min when samples collected in citrated tubes were left to sit as whole blood, but after 30 min, values remained stable for 1–7 h. Both R and MA values in citrated blood samples (after 30 min storage) were significantly smaller than those observed in fresh whole-blood samples [20]. Another study found that increasing storage time (over 30 min) of citrated samples resulted in a hypercoagulable pattern, with R times significantly shorter after 30 min of storage [21].

Based upon these studies, many centers using citrated whole-blood samples allow specimens to “rest” or sit for 30 min after blood draw in order to obtain consistent R and MA values. However, another study found that R times in citrated samples continued to decrease between 30 and 120 min [22]. Differences in patient populations, clot activators, and other factors make the studies difficult to directly compare. However, there remains uncertainty as to the best time point (after blood collection) to perform TEG analysis with citrated whole-blood samples. Changes in R and MA with increasing storage time may confound interpretation of TEG when citrated samples are used.

Three additional studies have observed apparent artifacts in TEG tracings, which may be linked to collection of samples in citrated tubes. One study noted what was concluded to be falsely increased
fibrinolysis when citrated samples were tested in heparinase cups from patients on extracorporeal membrane oxygenation (ECMO) or patients with ventricular assist devices [23]. Another study noted falsely increased fibrinolysis in the heparinase cup from patients with severe sepsis, although the authors did not specify whether fresh or citrated whole-blood samples were used for testing [24].

A third study specifically examined differences in TEG tracings (in both plain and heparinase cups) between fresh and citrated whole-blood samples for three patient populations. In healthy donors and patients after cardiopulmonary bypass, the only significant difference between fresh and citrated whole-blood tracings was the previously noted shortening of R time in citrated compared to fresh whole blood [25]. However, for some ECMO patients, collection of samples in citrate tubes resulted in apparent heparin reversal. For these patients, TEG tracings with fresh whole blood showed no clotting, whereas citrated whole-blood tracings were very similar to those produced by the fresh whole blood in the heparinase cup [25]. There remain concerns that testing of citrated whole-blood samples may result in a hypercoagulable profile in some patient populations; and caution should be exercised in using citrated blood samples in patient populations commonly treated with heparin.

Beyond choice of sample types and issues of timing between blood draw and testing, TEG and other viscoelastic tests are subject to unique pre-analytical and analytical artifacts that can significantly impact results. TEG is significantly more sensitive to the presence of heparin than most other coagulation tests. While this has advantages in certain clinical situations, it also means that in obtaining samples from patients being treated with heparin (therapeutically or to maintain catheter patency), great care must be used to avoid heparin contamination of samples. Combined plain and heparinase cup TEG analysis is recommended for any patients receiving heparin. TEG also requires manual pipetting and mixing of reagents, steps which may introduce greater variability in test results compared to automated assays. Viscoelastic tests are also subject to analytic errors from either pin slippage or vibration of the testing surface (Fig. 7). When TEG is performed point of care, it can be a significant challenge to insure that TEG values obtained from tracings with similar artifacts are not used for patient care.

With the unique pre-analytic and analytic issues associated with TEG testing, concerns have risen about whether TEG can produce standardized and consistent information across laboratories or healthcare settings. Only a handful of studies have systematically examined the inter-lab precision (reproducibility) of TEG results across laboratories or hospitals. The UK National External Quality Assessment Scheme (NEQAS) for Blood Coagulation published a study of external quality control (proficiency testing) using eight lyophilized plasma samples sent to 18 TEG users. Three samples were intended to represent normal coagulation, two samples were spiked with heparin to determine whether users could identify heparin effect (by comparing plain and heparinase TEG parameters), and three samples were manufactured factor-deficient samples intended to give no clotting [26]. Because the samples were lyophilized plasma (contained no platelets), data on MA (dependent primarily on platelet function) are difficult to interpret. Using the three normal samples, average coefficient of variation (CV) for R time between users was 15%–20% for plain cups and 38%–39% for heparinase cups. Using the heparinase cup for the two heparin-spiked samples, average CV for R time was 17%–29% (no clot was detected in the plain cup for heparin-spiked samples). Users were also asked to provide interpretations (normal or abnormal coagulation status) for each sample. Consensus between users for the normal samples was 27/31 (87%). All users reported abnormal coagulation for factor-deficient samples analyzed (33/33), and all users reported abnormal coagulation status for both heparin-spiked samples analyzed in plain cups (23/23). When asked to compare plain and heparinase cup results to determine whether heparin was present in a sample, 18/21 (86%) of heparin-spiked samples were correctly identified as containing heparin [26].

The College of American Pathologists (CAP) also offers proficiency testing for TEG using lyophilized samples. With nearly 300 laboratories participating in the 2013 TEG-A survey consisting of two samples: CVs for R time, MA and angle were all ≤11%, while CVs for K were ≤22% (CAP 2013 TEG-A survey summary). In another external quality assessment study, either frozen platelet-rich plasma or factor VIII-deficient plasma was sent to nine laboratories performing TEG for replicate analysis [27], with each lab performing measurements in duplicate on three different days for a total of 12 measurements at each site. For platelet-rich plasma, the between-lab CV for R and MA was 17% and 19%, respectively. However, K exhibited more variability (60% CV) while angle was the most reproducible parameter (CV 7%). Using the factor VIII-deficient plasma, between-lab precision for R was quite good (CV 9%), but CVs for the other TEG parameters varied between 22% and 47% [27]. In comparison, CAP coagulation surveys for routine tests such as PT and aPTT show <5% CV for most major instrument/reagent combinations. When asked to interpret whether a PT or aPTT was normal or prolonged, laboratories (~4000 labs) achieved >99% consensus (CAP 2013 CGL-A survey summary). Thus, TEG does not achieve levels of inter-laboratory consistency observed for routine coagulation testing. Further work is necessary to understand factors responsible for analytic variability and to standardize TEG testing within and across testing sites.

![Fig. 6. TEG® tracing artifact due to pin slippage during sample analysis.](image)
5. Conclusion

TEG and related viscoelastic tests provide simultaneous measurement of multiple aspects of whole-blood coagulation. Unlike conventional coagulation tests, interactions between cellular components and plasma components of the coagulation cascade are captured during viscoelastic testing. This allows definition of coagulation defects that are challenging to measure using routine coagulation assays. However, TEG and other viscoelastic tests are subject to a unique set of pre-analytic and analytic defects that impact test reliability and reproducibility. In addition, the increased sensitivity for heparin and coagulation factor deficiency, and imprecision of some parameters, may lead to erroneous treatment decisions in some clinical situations. TEG is a powerful analytic tool, but its implementation requires thought and planning to insure that the test is performed correctly and results are applied to patient populations that will benefit from identification of the coagulation defects measured.

References