

A Review of Thromboelastography

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Abstract: *The ability of blood to coagulate protects the body from life-threatening exsanguinations. This process is determined by a complex and balance between pro-coagulation factors, anticoagulants, and fibrinolysis. Major bleeding is a serious medical complication and an accurate and cost-efficient method of monitoring antithrombotic activity would be extremely useful. The commonly used blood tests to assess blood coagulation include prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), platelet count, fibrinogen concentration, D-dimer level, activated clotting time, and whole blood bleeding time (BT). However, there are delays in obtaining the results, especially when there is acute major bleed. These tests do not provide a complete picture of haemostasis like factor XIII, platelet function and the activity of the fibrinolytic system. While platelet count is part of a complete blood count, it does not reflect their function. TEG provides a representation of the sum of platelet function, coagulation proteases and inhibitors, and the fibrinolytic system. Analysis of the tracing provides a means to assess the need for blood component therapy as each element of the TEG tracing relates to a different aspect of clotting. TEG helps anesthesiologists monitor intraoperative bleeding and choose the most adequate blood transfusion products to achieve an optimal biological hemostasis. TEG provides a rapid point-of-care assessment of the coagulation process, with initial results available within 5 minutes. TEG is a promising diagnostic modality that offers several advantages compared to the other tests that have been mentioned above. TEG covers the entire field of hemostasis in the perioperative setting, from "platelet function" to fibrinolysis and also to monitor hypercoagulability. It has become so popular that many clinicians consider thromboelastography a self-sufficient coagulation test.*

1. Introduction

The ability of blood to convert from a liquid to a solid state, in other words, to coagulate, underlies the mechanism that protects the body from life-threatening exsanguination. This process of thrombosis is normally a localized event at the site of vascular injury while the rest of the circulating blood remains in a liquid state. Thrombosis is a dynamic process that includes thrombolysis to maintain or restore blood flow through vessels once an injury has been sealed. These unique properties of blood are largely determined by a complex and active balance between pro-coagulation factors, anticoagulants, and fibrinolysis. Two major pathologic conditions are commonly associated with a disequilibrium of this intricate system are bleeding and vessel thrombosis.

Normal physiologic hemostasis is achieved through the interplay of pro- and anti-coagulant properties of the vascular endothelium, platelets, and the coagulation cascade. Maintaining blood in a liquid state is critical for homeostasis. It allows blood to supply an adequate delivery of oxygen and nutrients to tissues while also eliminating carbon dioxide and other waste products.

Major bleeding is a serious medical complication that may be caused by external trauma, surgery, invasive procedures, or an underlying medical condition such as aneurysm rupture or peptic ulcer disease. According to the World Health Organization (WHO), injuries are responsible for 5.8 million deaths per year worldwide, with the associated bleeding responsible for about 30% to 40% of these deaths. (1)

A number of congenital disorders associated with a coagulation factor deficiency, such as Von Willebrand disease, hemophilia A or B, may cause significant bleeding

even with minor injuries. In addition, prescribed anticoagulants and antiplatelet agents may create a coagulopathic state that may lead to excessive bleeding either associated with trauma or medical procedures. Finally, major acute blood loss can lead to coagulopathy due to a loss of coagulation factors.

Venous thromboembolism (VTE) is another common and serious condition that is associated with abnormal blood coagulation. In these cases, systemic hypercoagulability shifts the body's homeostatic mechanisms toward a pro-thrombotic state. Routine coagulation testing has not been shown to predict such events, and in many cases, even a detailed hypercoagulability investigation fails to identify an underlying disorder. A large number of people take anticoagulants, antiplatelet agents and herbal medicines on a regular basis which impacts the accuracy of the results of many laboratory coagulation studies. (2)

Inadequate anticoagulation or antiplatelet therapy can lead to devastating thromboembolic conditions.

An accurate and cost-efficient method of monitoring antithrombotic activity would be helpful to maintain an acceptable risk/benefit ratio in trauma patients. Patients with ongoing or expected major bleeding would benefit from a reliable assessment of the functional state of the hemostatic system to provide optimal care, providing cost-effective replacement of only the needed blood components.

Conventional laboratory tests look at this system in a piecemeal fashion and give a limited indication of in vivo functionality. These tests take significant time for results, further limiting real-time usefulness. The commonly used blood tests to assess blood coagulation include prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), platelet count,

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fibrinogen concentration, D-dimer level, activated clotting time, and whole blood bleeding time (BT). These tests are usually used for the clinical diagnosis of coagulopathy and a possible prothrombotic state, to monitor anticoagulation therapy, and to assist in the treatment of bleeding episodes. More specific factor analyses, such as Factor V, proteins C and S, anti-thrombin III, anticardiolipin antibodies and prothrombin gene mutation are useful but not as readily available in emergency clinical situations.

Despite being very effective for specific clinical needs, such as anticoagulation monitoring, the first group of usual diagnostic tests has limitations. Their main disadvantage in circumstances of acute major bleeding is long turnaround time. Furthermore, they do not provide a complete picture of hemostasis due to their inability to assess some coagulation factors (such as Factor XIII), platelet function and the activity of the fibrinolytic system. Platelet concentration, easily measured as part of a complete blood count, does not necessarily reflect their function, especially in the presence of elements known to affect platelet reactivity, such as non-steroidal anti-inflammatory drugs, antiplatelet agents, uremia, malignancy, or alcohol intake. Bleeding time has a low sensitivity and high inconsistency in detecting platelet disorders. Delayed or inadequate diagnosis of coagulopathy in a bleeding patient may lead to an excessive and improperly balanced transfusion of scarce blood components with increased morbidity, treatment costs, and mortality.

Thromboelastography (TEG) was invented by Dr Helmut Hartert at the University of Heidelberg (Germany) in 1948. The first reported clinical application of the test occurred during the Vietnam War in an attempt to guide transfusions of blood components in injured soldiers. In 1980s, TEG was found to be beneficial in liver transplant patients, and in 1990s, was demonstrated to be useful in cardiac surgery. A more platelet-specific method in the form of the TEG Platelet Mapping system measures the platelet contribution to clot strength. The test works with whole blood but requires pipetting and cannot therefore be considered a true point-of-care assay. (3)

Pathophysiology of TEG

TEG is a non-invasive test that quantitatively measures the ability of whole blood to form a clot. The principle of this *in vitro* test is to detect and quantify dynamic changes of the viscoelastic properties of a blood sample during clotting under low shear stress. The test is performed in a specially designed system called a thromboelastograph consisting of 2 chambers simultaneously examining a blood sample in duplicate to reduce the risk of sampling and measurement errors.

The blood sample is collected via venepuncture in a plastic vial with 3.2% buffered sodium citrate with a citrate-to-blood ratio of 1:9. The vial is inverted several times to mix the blood and citrate. Maintaining this citrate-blood ratio is crucial for test accuracy. Citrate binds calcium, an important cofactor of coagulation, preventing the blood from clotting before the beginning of the test. A clotted specimen, reflecting a vial overfilled with blood, cannot be used. For TEG testing, the collected non-clotted samples are considered stable and usable for up to 2 hours at room

temperature. Non-citrated whole blood (native blood TEG or NATEM) can also be tested, but it must be used immediately. The test and reagents used are at room temperature. A volume of 340 μ L of citrated blood is pipetted to the study cup, recalcified by the addition of 20 μ L of 0.2M calcium chloride and then activated with a kaolin-cephalin reagent. Cephalins, or phosphatidylethanolamines, are a class of phospholipids commonly present in membranes of human cells. They are an important cofactor of the coagulation cascade which enables the assembly of tenase and prothrombinase complexes on the surface of platelets which are critical for thrombin generation. Kaolin is a mineral, primarily composed of hydrated aluminum silicate, which is a negatively charged molecule that can initiate the intrinsic coagulation pathway by activating Factor XII. Precise proportioning of the blood and kaolin-cephalin reagent is important for accurate and reproducible TEG results. Non-activated TEG is also possible, but the lack of activators significantly prolongs clotting time and the testing process which is not desirable in a clinical emergency.

Each chamber consists of a platform that holds a disposable cup where a blood sample is placed and a detection pin suspended in its center. The cup oscillates around the detection pin in a limited arc of plus or minus (+/-) 4 degrees 45' every 5 seconds. Induced pin movement is recorded and changes measured as a function of time. Initially, there is little movement of the pin since liquid blood possesses minimal viscosity and the oscillations of the cup are not transmitted to the pin. As the blood coagulates, it begins to adhere to both the cup and the pin and movement of the cup induces motion on the pin. (Fig 1)

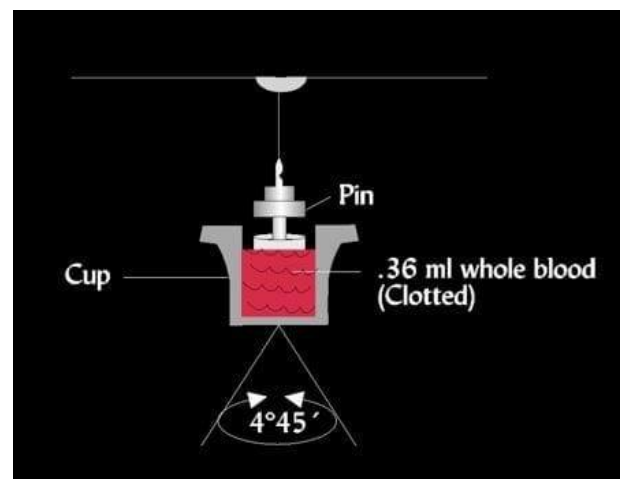


Figure 1: Pin and chamber configuration in TEG

These gradually increasing viscoelastic mechanical properties of the blood are reflective of the developing 3-dimensional fibrin mesh and platelet components of the clot. The greater the viscoelasticity of the clot, the higher the amplitude of the pin motion. As fibrinolysis starts, the fibrin-platelet structure begins to dissolve gradually, and the clot loses its contact with the detection pin which has less induced motion. The movement of the pin is transferred through the torsion wire to the electronic recorder, and the analyzer produces a tracing. Modern devices substitute a computer graphic for the old-style roller drum paper tracing. Newer version replaces the cup rotation method with a

resonance technique wherein the blood sample is subjected to vibration, and the vertical movement of the blood meniscus is measured under LED illumination. The system uses pre-measured cartridges that do not require pipetting and allows simultaneous performance of four blood tests. (4)

Rapid TEG (r-TEG) utilizes tissue factor instead of the kaolin-cephalin reagent to activate blood coagulation. Because tissue factor triggers the extrinsic coagulation pathway which involves a smaller number of coagulation factors, the test can be performed faster than conventional TEG. Rapid TEG can be completed within 15 minutes and thus is helpful in managing massive transfusions in trauma patients.

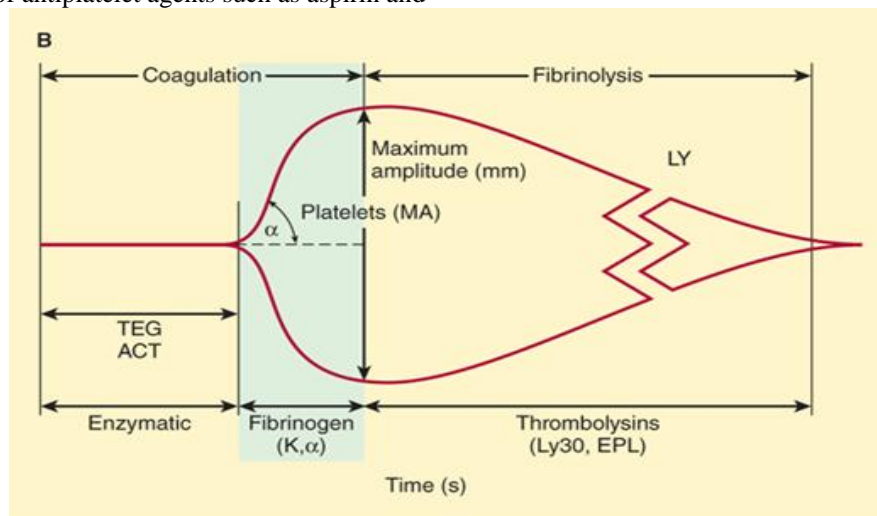
The TEG platelet mapping assay was developed to predict the inhibitory effect of antiplatelet agents such as aspirin and

clopidogrel. This is accomplished by evaluating platelet aggregation in the presence of adenosine diphosphate or arachidonic acid. TEG with added heparinase (hTEG) measures the effect of heparin reversal on blood coagulation.

Rotational thromboelastography, also known as rotational thromboelastometry (RoTEM) utilizes an oscillating pin which rotates +/- 4 degrees 45' every 6 seconds while maintaining the cup in a stable position

TEG Interpretation

The thromboelastogram (Figure 1) is a graphical image of the recorded amplitude of movement of the pin as a function of time. TEG measures the functional ability of the blood to make a hemostatic plug.



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Figure 2: A representative signature waveform of a normal TEG tracing

Fibrinogen is perhaps the most important protein in hemostasis, as the final stage of the coagulation cascade is converted to fibrin by thrombin and cross-linked by factor XIII. It also induces platelet activation and aggregation via binding to glycoprotein IIb/IIIa receptors on the surface of platelets, acting as the bridge for stable clot formation. During major bleeding, fibrinogen is the first clotting factor to reach critically low levels below the normal physiological level of around 2 to 4 g/L, which is associated with increased bleeding, coagulopathy, and in turn worsened clinical outcomes. Fibrinogen is an independent predictor of mortality in major trauma patients. Both Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM) have been increasingly used to diagnose fibrinogen deficiency and guide fibrinogen transfusion in trauma and surgical bleeding patients.

TEG has been used primarily to monitor blood component therapy during surgery. Initially used in hepatic transplantation, the technique has been used during cardiac surgery as well as damage control surgery after injury. Within 30 minutes, TEG provides a representation of the sum of platelet function, coagulation proteases and inhibitors, and the fibrinolytic system. Analysis of the tracing provides a means to assess the need for blood

component therapy. Each element of the TEG tracing relates to a different aspect of clotting, as follows: the time required for clot formation underscores the need for FFP, clot strength guides platelet therapy, addition of heparinase assists in determining protamine dosage, and the degree of clot lysis determines the need for antifibrinolytic therapy.

Parameters are presented on the tracing:

- **Reaction time**—The time in minutes elapsed from the start of the test until the clot moves the pin enough to produce a 2-mm amplitude on the tracing is defined as the reaction time (R). R reflects the activity of the coagulation cascade; a coagulation factor deficiency produces a prolonged R and hypercoagulability yields a shortened R time. The normal values for R depend on the type of clotting activator used. Prolongation of the R time reflects a quantitative or qualitative deficiency of coagulation factors that may be corrected by fresh frozen plasma (FFP) transfusion, prothrombin complex, or anticoagulant reversal
- **Alpha angle**—The alpha angle (α) is a measure in degrees of the speed of clot formation. i.e. reflects the conversion of fibrinogen to fibrin. It is defined as the angle between the horizontal axis of the tracing and the tangent to the tracing at 20-mm amplitude. Decreased

angles indicate a slower rate of clot strengthening, as seen with low fibrinogen levels. Normal values are in the range of 45°–55°. A depressed alpha angle could be treated with cryoprecipitate

- **Coagulation time**—The coagulation time (K) is measured in minutes from the end of R to when the tracing amplitude reaches 20 mm. Like the alpha angle, K is determined by the rate at which the clot. Prolongation of the K time, or a decrease of the alpha angle, suggests a deficiency of fibrinogen and may be corrected by cryoprecipitate or lyophilized fibrinogen concentrate.
- Low MA indicates a quantitative or functional deficiency of platelets and could be corrected by platelet concentrate transfusion or desmopressin. Finally, an increased LY value implies an activated fibrinolysis that may be treated by fibrinolysis inhibitors (aminocaproic or tranexamic acid). The opposite changes in TEG parameters suggest a prothrombotic state. This interpretive approach represents a convenient but rather simplified view on disturbances of blood coagulation. It is important to remember that due to the complex nature of hemostasis these TEG parameters are interrelated.

Advantages of TEG

TEG is widely used as a near-site hemostasis monitor because it is computerized, thromboelastography, easy to use and the results can be recorded and stored. It is considered a very helpful coagulation tool by a growing number of physicians, among whom anesthesiologists play a leading role. It helps anesthesiologists monitor intraoperative bleeding and choose the most adequate blood transfusion products to achieve an optimal biological hemostasis. (5, 6)

The development of nomograms by using thromboelastography variables has led to a substantial decrease in blood product transfusion in cardiac surgery, as compared with conventional tests

Clinical Significance

The main advantage of TEG testing is its potential to deliver immediate goal-oriented and individualized care to a bleeding patient:

- Global assessment of blood coagulability, including coagulation cascade, platelet function, and fibrinolysis
- Rapid real-time bedside test with a simple methodology (point-of-care testing)
- Diagnosis of coagulopathic bleeding
- Guide transfusion therapy and decrease the use of blood products
- Detect dynamic changes in blood coagulation during resuscitation
- Predict the clinical efficacy of therapeutic agents affecting blood coagulability (Fig 3)

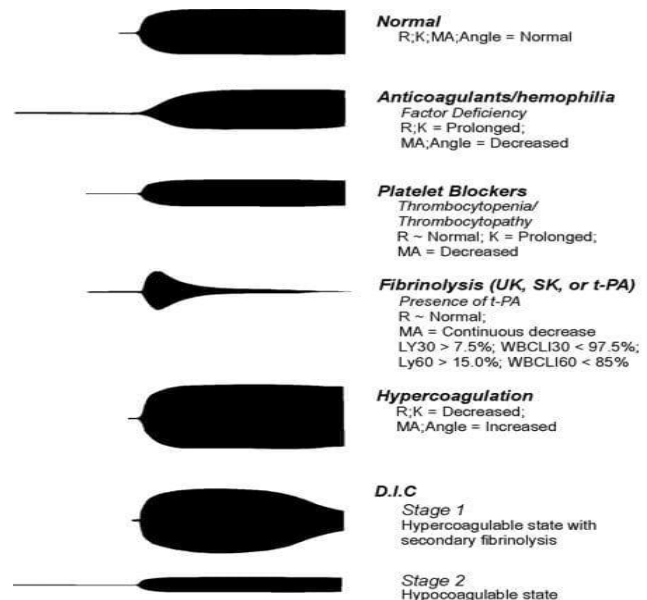


Figure 3: Important TEG patterns

TEG decreases blood product transfusions and surgical re-exploration due to postoperative bleeding in cardiac surgery patients. (7)

These effects were associated with a lower incidence of acute kidney injury and thromboembolic events. TEG/RoTEM decreases transfusion of blood components and reduces the overall mortality. TEG is also a more cost-effective method compared to standard coagulation tests in the diagnosis of coagulopathy in cardiac surgery.

TEG/RoTEM can diagnose coagulopathy and may predict blood components transfusion and mortality in trauma patients. (8)

TEG platelet mapping can detect platelet inhibition by clopidogrel and aspirin in surgical patients. A novel TEG-based scoring system has been suggested to diagnose disseminated intravascular coagulation. (9)

TEG may detect possible coagulopathy in patients with intracranial bleeding and hematoma enlargement. (10)

TEG may also have an application in liver disease patients. It is known that conventional coagulation tests are commonly abnormal in liver disease. At the same time, TEG/RoTEM results are normal in many patients despite an abnormal INR or platelet count due to adjustments in the system of hemostasis, or rebalanced hemostasis. Thus, TEG/RoTEM may provide a better insight into the risk of bleeding in patients with liver disease than conventional coagulation tests. (11)

2. Clinical Guidelines

Thromboelastography is recommended by NICE guidelines 2014 to help detect, manage and monitor hemostasis in cardiac surgery patients. Recently updated guidelines of the European Society of Anesthesiology recommended viscoelastic hemostatic assays (TEG/RoTEM) to guide the

management of perioperative bleeding and for managing severe peripartum hemorrhage

3. Limitations

Thromboelastography is not a conventional hemostasis test as it uses whole blood samples. It can be defined as a global nonspecific test, as compared with analytical coagulation tests (activated partial thromboplastin time, prothrombin time (PT), fibrinogen) which are performed with platelet-poor plasma.

Elderly patients demonstrate a tendency towards more pro-coagulable TEG results suggesting a need for correction of these reference values in elderly.(12)

In some circumstances, such as in patients undergoing cardiac surgery and liver transplantation, specific reference values are less important because the principal application of TEG is to compare the patient's own baseline to changes during the intraoperative and postoperative periods. In other clinical scenarios, such as trauma or postoperative bleeding, reference values are important for interpretation of the results as no baseline data is available. There is also some variability in testing results. Deviation of each of these TEG parameters from the reference values suggests specific disturbances of hemostasis and coagulation.

An ideal test on blood coagulation does not yet exist. TEG measures blood coagulation *in vitro*, with or without an additional activator. An important component of the coagulation cascade, tissue factor, cannot be quantified *in vitro*. Moreover, blood coagulation potential is only one component in such complex processes as clinical thrombosis and bleeding. Blood coagulation also depends on the size of the injured vessel, blood flow characteristics, and local vessel wall biology that determines the quantity and functional activity of the membrane-bound pro- and anticoagulation factors. In other words, there are significant aspects of coagulation which are not components of the blood. An abnormal TEG in a patient without clinically relevant bleeding does not require transfusion of blood components. A single test or patient-related factor rarely guide the decision to transfuse blood components or initiate/correct antithrombotic therapy.

TEG has a sensitivity and specificity that may vary significantly in different populations. In about half of patients on warfarin therapy, R-time may be normal in both TEG and rapid TEG tests, with a poor correlation between TEG and INR and INR remains the gold standard of monitoring warfarin therapy. Several important blood tests also cannot be currently replaced by TEG, such as P2Y12 platelet function assay to guide clopidogrel therapy, D-Dimer to exclude VTE in low-risk outpatients, and advanced thrombophilia diagnostic tests.

Anticoagulation and Antiplatelet Therapy

TEG implies activation of an intrinsic coagulation pathway with kaolin, it is sensitive to heparin and low molecular weight heparin therapy (R time). Prediction of platelet inhibition by antiplatelet agents (such as aspirin, clopidogrel, abciximab, eptifibatid, or tirofiban) is another promising

avenue for TEG application. Most antiplatelet agents are used with a standard dose despite several known issues associated with this approach. For example, up to 25% of patients with STEMI may be resistant to clopidogrel which increases the risk of recurrent cardiovascular events. Aspirin resistance has been associated with an increased incidence of myocardial infarction, stroke or death in patients with cardiovascular disease. Hence, there is significant variability in individual response to antiplatelet therapy. Available evidence does not support the use of usual laboratory testing to guide the dose of aspirin or clopidogrel. Future studies may determine if TEG can measure the effect of antiplatelet therapy, detect hyporesponsiveness, and predict the risk of bleeding or thromboembolic complications.

A novel concept of individualized health care applies to both anticoagulation and antiplatelet therapy monitoring. Using a standard dose of the same medications to treat patients with different medical conditions and comorbidities may not be an ideal approach. The potential of TEG to improve the quality of antithrombotic therapy is a promising avenue for experimental and clinical research.

Prevention of Venous Thromboembolism

Another potential application of TEG is to improve diagnosis, prevention, and treatment of patients with venous thromboembolism. TEG may be a useful tool to help with risk stratification. TEG may have a VTE predictive value in critically ill patients, gynecological oncology patients, and prostate cancer. Adult trauma patients have a 2-fold higher risk of VTE in patients with hypercoagulable TEG parameters on arrival to the trauma bay. TEG is however, of less value in predicting VTE in orthopedic surgery. R time of TEG is significantly shorter in critically ill patients on LMWH prophylaxis who develop DVT compared to those patients who do not. Thus, TEG may be helpful to predict VTE that occurs despite standard pharmacological prophylaxis.

4. Conclusions

Thromboelastography is a comprehensive assay of the overall clotting process and overcomes the problems of determining deficiencies in the clotting mechanism. TEG provides a rapid point-of-care assessment of the coagulation process, with initial results available within 5 minutes. TEG measures viscoelastic changes of clot formation through clot lysis, evaluating the integrity of the coagulation system, platelet function, fibrin polymerization, clot strength, and fibrinolysis. Results of TEG permit targeted transfusion and TEG is used in liver transplant, cardiac bypass, and, increasingly, trauma and general surgery. Thromboelastography (TEG) is a promising diagnostic modality that offers several advantages compared to the other tests that have been mentioned above. TEG covers the entire field of hemostasis in the perioperative setting, from "platelet function" to fibrinolysis and also to monitor hypercoagulability. The test has become so popular that many clinicians consider thromboelastography a self-sufficient coagulation test.

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