Chapter 1

TEG® Design and Principles of Operation

Indications for Use

The Thrombelastograph® (TEG®) Hemostasis System 5000 series is a non-invasive diagnostic instrument designed to monitor and analyze the coagulation state of a blood sample in order to assist in the assessment of patient clinical hemostasis conditions. The TEG® analyzer is indicated for use with adult patients where an evaluation of their blood coagulation properties is desired. Coagulation evaluations are commonly used to assess clinical conditions such as post-operative hemorrhage and/or thrombosis during and following cardiovascular surgery, organ transplantation, trauma, and cardiology procedures.

Intended Use

The TEG® 5000 series analyzer is intended to be used to provide a quantitative and qualitative indication of the coagulation state of a blood sample by monitoring, measuring, analyzing, and reporting coagulation parameter information. The TEG® analyzer records the kinetic changes in a sample of whole blood, plasma or platelet rich-plasma as the sample clots, retracts, and/or lyses (breaks apart).

Results from the TEG® analyzer should not be the sole basis for a patient diagnosis; TEG® results should be considered along with a clinical assessment of the patient's condition and other coagulation laboratory tests. For Professional Use Only.

Introduction

This manual describes how to use the Thrombelastograph® (TEG®) Hemostasis System 5000 series and higher using Version 4 TEG Analytical Software (TAS™).

Application of the TEG® analyzer has been described in articles published in many of the most prestigious peer-reviewed journals. All suggested treatments are based on the experiences of clinicians who have used them successfully and published their results. References are found at the end of each chapter.

This introduction outlines some of the various analytical techniques that can provide additional information on a blood sample. Most of the techniques

have evolved from over 1000 research publications in the last 20 - 30 years, with the greatest increase in applications occurring in the last five years. The most outstanding results have been demonstrated for the management of hemostasis during major surgical interventions such as liver transplants and cardiopulmonary bypass procedures. Concomitantly, recent advances in the understanding of the biochemistry of coagulation have supported the advantages of whole blood TEG® analysis by demonstrating the role of cell surfaces in localization, amplification, and modulation of coagulation functions[1]. As a result of this knowledge, the TEG® analyzer has evolved from a research tool into a powerful clinical monitor to evaluate the interaction of platelets and plasma factors, plus any additional effects of other cellular elements (e.g., WBCs, RBCs, etc.) with the activities of the plasma factors.

The discussion of the techniques will be centered around their current application to liver transplantation and cardiopulmonary bypass. The most commonly used sample types and techniques and their advantages are listed later in table 1 on page 11.

The TEG® system is comprised of the TEG® Hemostasis System together with the TEG® Analytical Software. This package provides breakthrough capabilities such as simultaneous analysis of up to eight samples, automatic calculation of a wide range of coagulation parameters, and data management facilities. The software can be run in a configuration that allows the analyzer to be placed in a centralized location such as a laboratory, with results displayed where needed, for example, in remote operating rooms. A full description of the TEG® Analytical Software can be found beginning in Chapter 4.

TEG® Design Principles

The TEG® analyzer's approach to the monitoring of patient hemostasis is based on these two facts:

1. *The end result of the hemostasis process is a single product — the clot.*
2. *The clot's physical properties (rate, strength, and stability) will determine whether the patient will have normal hemostasis, will hemorrhage or will develop thrombosis.*

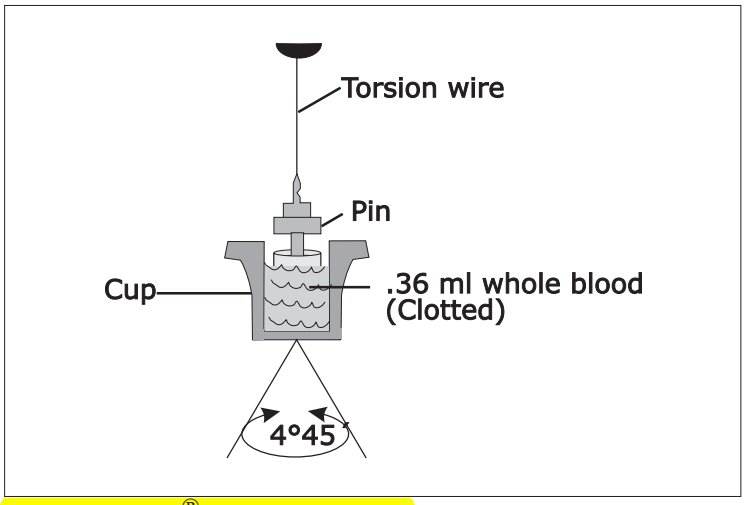

Figure 1.1. TEG® sample cup design

The TEG® analyzer measures the clot's physical property by the use of a special stationary cylindrical cup that holds the blood and is oscillated through an angle of 4°45´ (Figure 1.1). Each rotation cycle lasts 10 seconds. A pin is suspended in the blood by a torsion wire and is monitored for motion. The torque of the rotating cup is transmitted to the immersed pin only after fibrin-platelet bonding has linked the cup and pin together. The strength of these fibrin-platelet bonds affects the magnitude of the pin motion, such that strong clots move the pin directly in phase with the cup motion. Thus, the magnitude of the output is directly related to the strength of the formed clot. As the clot retracts or lyses, these bonds are broken and the transfer of cup motion is diminished.

The rotation movement of the pin is converted by a mechanical-electrical transducer to an electrical signal which can be monitored by a computer.

The resulting hemostasis profile is a measure of the time it takes for the first fibrin strand to be formed, the kinetics of clot formation, the strength of the clot (in shear elasticity units of dyn/cm^2) and dissolution of clot (Figure 1.2).

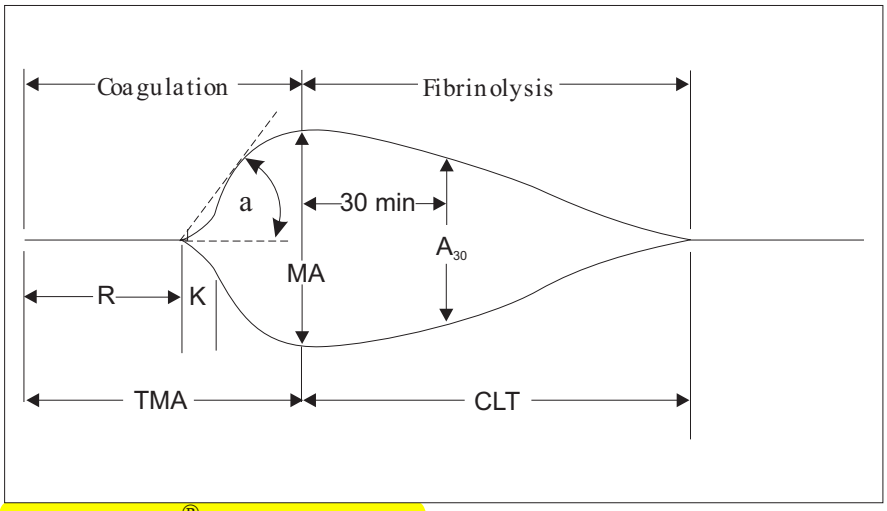

Figure 1.2. TEG® tracing parameters

Performance Characteristics and Specifications

Performance characteristics and specifications for the TEG® analyzer are detailed in Appendix A.

TEG® Theory

The computerized Thrombelastograph® Hemostasis System (TEG®) automatically records the kinetic changes in a sample of whole blood, plasma, or platelet-rich-plasma as the sample clots, retracts and/or lyses (breaks apart). The resultant coagulation profile is therefore a measure of the kinetics of clot formation and dissolution and of clot quality.

The TEG® analyzer monitors shear elasticity, a physical property of a blood clot, and is, therefore, sensitive to all the interacting cellular and plasmatic components in the blood that affect the rate or structure of a clotting sample and its breakdown. The clot's ability to perform useful mechanical work (the work of hemostasis) is a function of the net result of the interactive coagulation proteins and cellular elements involved in the process of hemostasis. In essence, the TEG® analyzer measures the ability of the clot to perform mechanical work throughout its structural development.

The overall coagulation profile can be qualitatively or quantitatively interpreted in terms of the hypo-, normal, or hypercoagulable state of the sample and the degree of lysis.

TEG® Parameters

To evaluate the graphic information displayed by the TEG® analyzer, five main parameters of clot formation and lysis are measured (See Figure 1.2):

R	R time is the period of time of latency from the time that the blood was placed in the TEG® analyzer until the initial fibrin formation. This represents the enzymatic portion of coagulation.
K	K time is a measure of the speed to reach a certain level of clot strength. This represents clot kinetics.
α	α measures the rapidity of fibrin build-up and cross-linking (clot strengthening). This represents fibrinogen level.
MA	MA, or Maximum Amplitude, is a direct function of the maximum dynamic properties of fibrin and platelet bonding via GPIIb/IIIa and represents the ultimate strength of the fibrin clot. This represents platelet function/aggregation.
LY30	LY30 measures the rate of amplitude reduction 30 minutes after MA. This represents clot lysis.

The four coagulation parameters (R, K, α, MA) can be combined to yield indices of coagulability, while additional measurements can be made to evaluate other aspects of the coagulation profile such as time to MA and time to lysis as described below.

R or R-Time

Reaction Time. The time from the start of a sample run until the first significant levels of detectable clot formation (amplitude = 2mm in the TEG® tracing). This is the point at which most traditional coagulation assays reach their end-points. R-time is prolonged by anticoagulants and factor deficiencies and shortened by hypercoagulable conditions.

K or K-time

Achievement of a certain clot firmness. The time from the measurement of R (beginning of clot formation) until a fixed level of clot firmness is reached (amplitude = 20 mm). Therefore, K-time is a measure of the speed or clot kinetics to reach a certain level of clot strength. K is shortened by increased fibrinogen level and, to a lesser extent, by platelet function, and is prolonged by anticoagulants that affect both. If the amplitude does not reach 20mm, K is undefined.

Angle (α)

The kinetics of clot development. The angle is closely related to K-time, since they both are a function of the rate of polymerization. The angle is more comprehensive than K-time, since there are hypocoagulable conditions in which the final level of clot firmness does not reach an amplitude of 20 mm (in which case K is undefined). Similar to K, α is larger by increased fibrinogen levels and, to a lesser extent, by platelet function, and is decreased by anticoagulants that affect both.

MA

Maximum Amplitude. Measurement of maximum strength or stiffness (maximum shear modulus) of the developed clot. Clot strength is the result of two components — the modest contribution of fibrin to clot strength and the much more significant contribution of the platelets.

Other clot formation parameters

In addition to the major parameters just described, several others can aid in determining clot kinetics, strength, and stability:

- ❒ projection of MA expressed as the PMA parameter
- ❒ time to MA expressed as the TMA parameter
- ❒ amplitude, clot strength at a specific time expressed as the A parameter
- ❒ shear elastic modulus strength expressed as the G and E parameters
- ❒ thrombodynamic index expressed as the TPI parameter

PMA

PMA - Projected MA, an estimator of MA, that is, whether the MA value will achieve at least the lower limit of the normal value for samples treated with Kaolin or Celite (see the section named “Blood sample types” later in this chapter). PMA facilitates earlier detection of platelet dysfunction and earlier therapy decisions before MA is available.

PMA begins to display when amplitude reaches 5 mm, and is finalized when the rate of clot formation slows (α is final). PMA is displayed as either:

- ❒ **0** (to indicate that it is likely that MA will reach the lower limit of normal)
- ❒ **1** (MA is unlikely to reach the lower limit of normal).

Once the MA value approaches the lower limit of normal, it should be used for evaluation instead of PMA.

Time to MA

TMA - Time to MA, a global measurement of the dynamics of clot kinetics. TMA combines the rate of clot development from the start of a sample run until the clot reaches its maximum strength. This can be described as the time needed to form a stable clot.

A parameter

The A parameter measures the width of the tracing at the latest time point. It is equal to MA until MA is determined. Amplitude (A) is a function of clot strength or elasticity and is measured in mm.

G parameter

The A parameter can be transformed into the actual measure of clot firmness (G) (shear elastic modulus strength, SEMS) and is measured in dyn/cm² (displayed in the software as d/sc). The absolute SEMS of the sample can be calculated from A as follows:

$$G = 5000A/(100-A)$$

Note that A is equal to MA until MA is reached, at which time calculation of G stops. The elastic shear modus G of the sample increases exponentially in proportion to the amplitude (A) of the TEG® tracing.

An amplitude of 50 mm (normal value of whole blood) corresponds to a SEMS of 5000 dyn/cm². An increase in A from 50mm to 67 mm is equivalent to a two-fold increase in the SEMS. Thus, the G parameter not only provides a measurement of clot firmness in dym/cm² units, but also is more indicative of

small changes in the clot strength or clot breakdown than is the amplitude in mm because it is an exponential reflection of A.

E parameter

E is a normalized G parameter and is referred to as an elasticity constant. Instead of 5000A it is replaced by 100A. (Note that A is equal to MA until MA is reached.) The rationale behind this index is that at the amplitude of 50 mm (normal value of whole blood), the E is (100*50)/(100-50) = 100. Therefore E provides a relative elastic scale in which a normal clot with a maximum elastic modulus of 50 mm is given an elastic modulus of 100. E is expressed as dyn/cm^2.

Thrombodynamic Potential Index

TPI=EMX / K, relative elastic shear modulus divided by the kinetics of clot development, where EMX is E at maximum amplitude (MA), i.e., EMX = (100*MA)/(100-MA), and K is measured in mm. This parameter was proposed by Raby[2,3]. According to Raby[3], TPI describes the patient's global coagulation whether the patient is normal coagulable (TPI between 6 - 15), hypocoagulable (TPI < 6), or hypercoagulable (TPI >15), when using sodium citrated native whole blood. The utility of this parameter is demonstrated by Szefner et al[3] and Copeland et al[4] in the monitoring of the hemostasis of patients undergoing total artificial heart or heart assist device implantation.

The Coagulation Index

A Coagulation Index (CI) that describes the patient's overall coagulation is derived from the R, K, MA and Angle (α) of native or kaolin/celite-activated whole blood tracings.

Normal values for the Coagulation Index lie between -3.0 and +3.0, which is equivalent to three standard deviations about the mean of zero.

Positive values outside this range (CI > +3.0) indicate that the sample is hypercoagulable, whereas negative values outside this range (CI < -3.0) indicate that the sample is hypocoagulable.

Hypercoagulable conditions like cancer (adenoma) or monitoring deep-vein thrombosis are detected at CI values of +5.0 and above[8,9].

Preliminary equations involving whole blood, Celite-activated whole blood, or both combined are available[7,8]. The equations should be validated before applying them clinically. Since the normal range of sodium citrated blood is very similar to non-citrated blood, the same coefficients are applied to sodium citrated native and celite blood as best estimates.

The equation for the TEG® coagulation indices are simple linear combinations of the variables as follows:

Index	Equation
Native Whole Blood	$CI = -0.2454R + 0.0184K + 0.1655MA - 0.0241\alpha - 5.0220$
Celite-activated WB	$CI = -0.6516R_c - 0.3772K_c + 0.1224MA_c + 0.0759\alpha_c - 7.7922$
Combined	$CI = -0.112R - 0.222K + 0.040MA - 0.042\alpha - 0.578R_c + 0.370K_c + 0.111MA_c + 0.097\alpha_c - 8.397$

Note: R and K values must be in min. Parameters that have the subscript "c" are measured for Celite-activated samples. Also note: when MA < 20 mm, K is undefined and CI is not calculated.

Cohen et al[7] compared TPI with CI in a study involving cancer patients, and found that the CI is very close to TPI, but is a slightly better discriminator between hyper- and normal coagulable in this population. This is perhaps due to the contribution of the R and α parameters in the CI equation.

Clot Lysis Parameters

Several methods have been proposed to evaluate clot lysis.

It should be noted that a clinical fibrinolytic state involves the presence of tissue plasminogen activator (t-PA), which produces fibrin degradation products.

Characteristically, fibrinolysis leads to clot dissolution, depending on the severity and stage (early or late) of the fibrinolytic process. Therefore, several sets of parameters are computed to quantify the fibrinolytic state. They are similar in that they rely on the loss of clot strength with time after the maximum clot strength (MA) is reached:

- ❒ reduction in area measurements expressed as the LY30 and LY60 parameters
- ❒ reduction in amplitude measurements expressed as A30 and A60 parameters
- ❒ estimated percent lysis expressed as the EPL parameter
- ❒ clot lysis time expressed as the CLT parameter

LY30 and LY60

The LY30 and LY60 parameters measure percent lysis at 30 minutes and 60 minutes after MA is reached. The LY30 and LY60 measurements are based on the reduction of the area under the TEG® tracing from the time MA is measured until 30 (or 60) minutes after the MA.

A30 and A60

The A30 and A60 parameters are the amplitudes of the TEG® tracing at 30 minutes and 60 minutes after MA is measured.

A30 and A60 are point measurements that look only at the TEG® tracing amplitude A at 30 and 60 minutes after MA. LY30 and LY60, on the other hand,

are measures of the area under the TEG® tracing, and, therefore, contain more information because they look at the entire tracing between MA and 30 (or 60) minutes after MA.

A30 and A60 are sometimes presented in an alternate form called the Whole Blood Clot Lysis Index (CL30 or CL60), which presents the values of A30 or A60 relative to MA. The formulas are:

$$CL_{30} = 100 \times (A_{30} / MA)$$
$$CL_{60} = 100 \times (A_{60} / MA)$$

The smaller the value of CL30 or CL60, the greater the severity of the fibrinolytic process. Note that CL30 and CL60 measure fibrinolysis inversely to the way it is measured by the LY30 and LY60 parameters. Generally, when LY30 and LY60 are high (i.e., fibrinolytic activity is high), CL30 and CL60 are low, and vice versa.

You can convert CL30 or CL60 to be proportional to the level of fibrinolytic activity with the formula:

$$CL30' = 100 - CL30 = 100 \times (MA - A_{30}) / MA$$
$$CL60' = 100 - CL60 = 100 \times (MA - A_{60}) / MA$$

The two TEG® tracings in Figure 1.3 illustrate the significance of the LY parameters relative to the CL parameters:

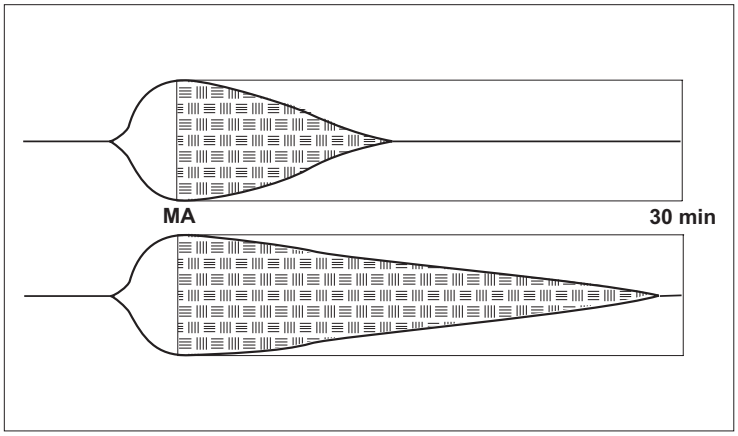

Figure 1.3. CL30 parameter

Thirty minutes after MA is reached, the amplitudes of both tracings read zero due to fibrinolytic activity. Therefore, using the formulas on the previous page, the CL30 parameter for both tracings is zero. In this instance, the CL30 parameter is of no use in differentiating the two tracings.

However, the LY30 parameters for the two tracings are radically different. In the top tracing, the shaded area under the curve is approximately 15% of the rectangular area. (The rectangle represents the area under the curve if there

had been no fibrinolysis.). Thus, LY30 is approximately 85%. In the bottom tracing, the shaded area comprises about 85% of the rectangle. This makes the value of LY30 approximately 15%.

Thus, CL30 and CL60 represent point measurements of the fibrinolytic status at exactly 30 and 60 minutes after MA is achieved. LY30 and LY60 represent the fibrinolytic process that took place during those 30 or 60 minutes.

The lysis parameters are illustrated in Figures 1.2 and 1.3

Estimated Percent Lysis

Estimated Percent Lysis (EPL) is the estimated percent lysis at 30 minutes after MA. This parameter is computed 30 seconds after the MA, and is continually updated until 30 minutes after MA is reached, when EPL becomes equal to LY30. This parameter gives an idea of the percent lysis prior to 30 minutes after MA. EPL is computed by finding the slope connecting MA to any point between MA and 30 minutes after, then extrapolating to A30. EPL is then 100(MA-Â$_{30}$)/MA, until A30 is reached and it becomes equal to LY30.

Clot Lysis Time

Clot Lysis Time (CLT) is the elapsed time between MA and 2 mm amplitude or less post MA.

Lysis Time Estimate

Lysis Time Estimate (LTE) is an estimate of CLT. It is computed 30 seconds after MA and is continually updated until 60 minutes after MA or when an amplitude is reached, whichever comes first. If LTE is greater than three hours, the value is displayed as ">3 hrs." LTE is derived by calculating the slope of the tracing and extrapolating to an amplitude of 2 mm.

Blood Sample Types

The following sections describe the various sample preparations that can be used with the TEG® analyzer and the conditions under which to use the different blood modifiers. The actual sample preparation for analysis is described in Chapter 11.

Table I		
Sample Type	**Blood/Reagent**	**Purpose**
Native	Native whole blood (NWB)	Global evaluation of coagulation
Activated	NWB & Celite, TF, Kaolin, Thrombin, DAPTTIN, etc.	Speed analysis
Antifibrinolytic drugs	WB & εACA, Aprotinin, Tx	Reverse fibrinolysis
Heparinase	WB & Heparinase	Reverse heparin effects
Citrated	Citrated WB (CWB)	Prolonged storage
Activated citrated	CWB & Celite, Kaolin, TF, Thrombin, DAPTTIN, etc.	Speed analysis
PRP	Citrated Platelet Rich Plasma	Enriched platelet function
PPP	Citrated Platelet Poor Plasma	Plasma coagulation
Platelet blockers	WB & ReoPro, Integrilin, Aggrastat, Plavex, etc.	Reduced or abrogated platelet function

Native Whole Blood Coagulation Samples

In general, the basic TEG® measurements of kinetics, strength and stability of a coagulum can be determined by using a native whole blood sample. This method has provided the most sensitive method for monitoring hypercoagulation or fibrinolytic conditions.

This type of sensitivity does not mean this sample type is the most practical, and we will see how more practical techniques can provide similar results.

Modified Native Whole Blood Samples

Native whole blood samples can be modified by addition of reagents to the *in vitro* sample to determine if a possible therapy might be effective for a coagulopathy, to improve speed of analysis, or to reverse a clinical condition (e.g., heparinization).

These techniques involve addition of the following reagents to the native whole blood sample:

- ❒ Activators (Celite, Kaolin, tissue factor, thrombin, DAPTTIN, etc.)
- ❒ Heparin neutralizers (Heparinase, protamine)
- ❒ Platelet blockers (ReoPro®, Integrilin®, Aggrastat®, etc.)
- ❒ Antifibrinolytic drugs (Epsilon-amino-caproic acid, tranexamic acid, aprotinin)

Activators

Celite- or Kaolin-activated TEG® methods are used to reduce variabilities and to reduce the running time of a native whole blood TEG® sample by as much as half—except for patients on aprotinin (Trasylol). Celite, silica particles (diatomaceous earth), shortens coagulation time because it acts as a contact surface activator (intrinsic pathway), which activates Factor XII and platelets and stimulates the reserve clotting ability of a blood sample. Similar to celite is kaolin (hydrated aluminum silicate), which also activates the intrinsic pathway via Factor XII.

Tissue Factor (TF) is an enzyme that, together with factor VII, shortens coagulation time by activating factors IX and X (extrinsic pathway).

Thrombin is an enzyme that shortens coagulation time (common pathway) by cleaving fibrinogen to form the fibrin clot, and activates platelets.

Heparin Neutralizers

Heparinase I, from *Flavobacterium heparinum*, is an enzyme that rapidly and specifically neutralizes the anticoagulant properties of heparin. Heparinase acts by cleaving the heparin molecule into small inactive fragments without affecting the function of other blood components involved in coagulation.

Adding heparinase to the blood allows visualization of any developing coagulopathies during perioperative cardiopulmonary bypass that are masked by high levels of therapeutic heparin or are masked by heparin released from the mask cell of the donor liver during liver transplantation.

Compare the R parameter of heparinase-modified TEG® samples and non-heparinase-modified samples for patients undergoing cardiopulmonary bypass surgery or liver transplantation. If the R parameters are the same, enough protamine was given to neutralize all administered heparin, in the case of CPB or endogenic heparin during liver reperfusion stage.

Heparinase also eliminates any problems or concerns associated with drawing blood from a heparinized line. Under these circumstances, heparinase will correct, *in vitro*, a prolonged onset of clotting compared to a control sample.

Platelet Blockers

Since all platelet-fibrin(ogen) interaction is mediated by the platelet integrin GPIIb/IIIa receptor, it is possible to negate the platelet contribution to TEG® tracing with anti-platelet drugs such as c7E3 Fab (ReoPro®), an antibody fragment that inhibits clot retraction and abolishes platelet aggregation by binding to fibrin(ogen) receptors GPIIb/IIIa on platelets. Adding a platelet blocker drug to a whole blood sample can be used to measure the effect of platelets on the TEG® profile.

Antifibrinolytic Drugs

Adding Amicar or the more powerful tranexamic acid or aprotinin (Trasylol) *in vitro* to a whole blood sample has been used to identify how a previously identified fibrinolytic TEG® profile will respond to this inhibitor. The concentration of antifibrinolytic agents used in vitro are in proportion to the recommended in vivo therapy[5,6].

Aprotinin inhibits activation of kallikrein and will cause some anticoagulation of the TEG® profile with celite activated samples. Specifically, aprotinin will increase the R parameter by approximately 10 percent, unless the sample is drawn within 30 minutes of a high loading dose (2.0 million KIU). For samples drawn after 30 minutes of high-dose aprotinin, you may see the R as a straight line; therefore, it is better to use kaolin, which is not affected by aprotinin, instead of/in addition to treating samples with celite.

Sodium-Citrated Whole Blood Samples

Citrated TEG® samples are used for conditions where it is difficult to transport the native or modified whole blood to the TEG® sample within four to six minutes of phlebotomy. The citrated TEG® sample requires a citrated whole blood specimen, which is recalcified at some later time. See the section on preparing sodium citrated samples, beginning on page 131 named "Citrated Whole Blood TEG® samples."

Sodium citrated techniques are also useful when using differential centrifugation to isolate platelet-poor plasma (PPP TEG®) or platelet-rich plasma (PRP TEG®). Normal ranges can be established for each of these analyses so that the specific attributes of coagulation can be monitored.

A good example of this technique is to run a whole blood and a PPP TEG® tracing. The differences in these two tracings are the result of removing the cellular elements such as the platelets. This is an excellent way of quantifying the effects of the platelets. However, using ReoPro, Integrilin, or Aggrastat in vitro, you can accomplish the same without the need for centrifugation.

Finally, all the modified native whole blood techniques can also be applied to a citrated whole blood sample.

Data Analysis

The TEG® tracing can be qualitatively or quantitatively analyzed. The patterns are easily interpreted without measurement to determine conditions of hyper-, hypo-, normal coagulation, and fibrinolysis. However, by using the measurements and established normal ranges and indices, the patterns can be quantified as to the degree of abnormality, as described in Chapter 2. This allows therapies to be judged for their effectiveness in correcting a pathological state.

Qualitative Analysis

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

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Chapter 2

Hemostasis

Components of Hemostasis

Hemostasis is a dynamic, extremely complex process, involving many interacting factors, which include coagulation and fibrinolytic proteins, activators, inhibitors, and cellular elements (e.g. platelet cytoskeleton, cytoplasmic granules and platelet cell surfaces).

The ideal way to treat a bleeding or prothrombotic patient is to measure the net product of the multitude of the interacting factors and cellular elements and their interactions in the shortest time possible.

Without this, the clinician has no choice but to use prophylactic drugs in spite of the cost and possible side effects to reduce the probability of coagulopathy, and when coagulopathy does occur he is compelled to do guess work or to give a variety of blood components and hope the result is positive. Researchers and clinicians have been looking for a way to effectively measure and treat patient hemostasis and to enable them to monitor a new class of platelet blockers that have either recently been introduced or are being evaluated.

However, the clinician can be provided with precise information to properly treat the bleeding or clotting patient most effectively and in the shortest time possible if the following is considered:

Tools for the Clinician

The tools (or variations of these) available to the clinician for the treatment of coagulopathy are as follows:

- Blood components:
  - Fresh frozen plasma (FFP)
  - Cryoprecipitate (cryo)
  - Platelets

- ❒ Antifibrinolytic drugs:
  - Aminocaproic acid (Amicar®)
  - Aprotinin (Trasylol®)
  - Tranexamic acid (Tx)
- ❒ Thrombolytic drugs:
  - rt-PA
  - Urokinase
  - Streptokinase
- ❒ Platelet blocker drugs:
  - ReoPro®
  - Integrilin®
  - Aggrastat®
  - Plavix®
  - Aspirin
  - Etc.

Functional Hemostasis

Despite the many components entering into hemostasis, two facts override all others:

- ❒ *The end result of the hemostasis process is a single product — the clot.*
- ❒ *The clot is a mechanical device.*

The resulting clot

Once the coagulation cascade is activated, whether through the intrinsic pathway, the extrinsic pathway, or a combination of both, thrombin is formed. The thrombin cleaves soluble fibrinogen into fibrin monomers, which spontaneously polymerize to form protofibril strands that undergo linear extension, branching, and lateral association leading to the formation of a three dimensional network of fibrin fibers. A unique property of this network structure is that it behaves as a rigid elastic solid, capable of resisting deforming shear stress of flowing blood[1].

Resistance to the deforming shear stress of the network of fibrin fibers is enhanced further by platelets, which are also activated by thrombin.

Platelets achieve this in two ways:

Stabilizing the fibrin network structure

Platelets enhance fibrin polymerization by acting as nodes or network branch points. They stabilize and significantly enhance the structure rigidity of the fibrin network.[1]

Platelet contractility force

Platelet GPIIb/IIIa receptors bind the polymerized fibrin network to the platelets' actin cytoskeleton. Actin is a muscle protein that has the property of transmitting contractility force. Platelets, through GPIIb/IIIa receptor, transmit their contractility force to the fibrin network by exerting a "tugging" force and thus affect the mechanical strength of fibrin[1]. The contractility force is the major contributor to the strength of the clot[1,10.] Therefore, the end result of the activated hemostasis is the fibrin strand, which, together with activated platelets, via GPIIb/IIIa receptors, forms fibrin-platelet bonding to produce the final clot.

The clot as a mechanical device

The kinetics, strength, and stability (rate of dissolution) of the clot, that is, its physical properties to resist deforming shear stress of the flowing blood, determine its capacity to do the work of hemostasis, which is to stop hemorrhage and prevent thrombosis. In essence, the clot is a damage-control device, a temporary stopper, which gradually dissolves during vascular recovery.

The clot is the elementary machine of hemostasis, and the TEG® analyzer measures the ability of the clot to perform mechanical work throughout its structural development.[2]

Interrelationship of Parameters

The TEG® analyzer, using a small blood sample of whole blood, measures the net product of the interaction of platelets with protein coagulation cascade from the time of placing the blood in the TEG® analyzer until initial fibrin formation, clot rate, strengthening, and fibrin-platelet bonding via GPIIb/IIIa, to eventual clot lysis. Time, rate, strength, and stability of clot indicate whether the patient has normal, hypo-, or hypercoagulable hemostasis, and provide an indication of treatment necessary to normalize it. The following section explains in detail how this is done.

Each TEG® parameter, R, K, α, MA and LY30, represents a different aspect of the clot's physical properties. However, due to the interactive nature of hemostasis, these parameters are interrelated. In general, an elongated R means that it takes longer for the first fibrin strand to be formed and therefore an elongated R represents a deficiency in coagulation factors, inhibitors, and/or activators, which results in a slow rate of thrombin generation.

The α parameter measures the rapidity (kinetics) of fibrin buildup and cross-linking, that is the speed of clot strengthening. K, or K time, is a measure of the rapidity of reaching a certain level of clot strength (20 mm amplitude). K and α both measure similar information and both are affected by the availability of fibrinogen, which determines the rate of clot buildup, and, to a

lesser extent, by platelets. Therefore, an elongated K and a reduced α represents a low level of fibrinogen. According to Kang, six units of cryo increased fibrinogen level by 37 ml/dl and increased clot formation rate , α, by 9.4 degrees[7]. MA measures the strength of clot and is affected by platelet number and function and, to a lesser extent, by fibrinogen level. Therefore, a small MA and normal R, K, and α represents thrombocytopenia or platelet dysfunction. According to Kang's study mentioned above, ten units of platelets increased platelet count by 40,200±31,400/mm^3 and increased MA by 13.2mm[7]. However, MA, K, and α are interrelated due to the interaction between fibrinogen fiber and platelets, which together form the fibrin-platelet bonding to produce the final clot. A low level of fibrinogen will be compensated for, to some extent, by a high level of platelet function, and vice versa.

All studies in the above-cited references were conducted on patients undergoing liver transplantation or cardiopulmonary bypass, and native blood samples were used.

LY30 greater than 7.5% represents hyperfibrinolysis.

Note: In our analyses we assume that the patient is not being treated with heparin or low molecular weight heparin. If he is, then the TEG® sample should be treated with heparinase to neutralize the effect of heparin.

An example

A TEG® schematic output demonstrates the above and the interactive nature of hemostasis:

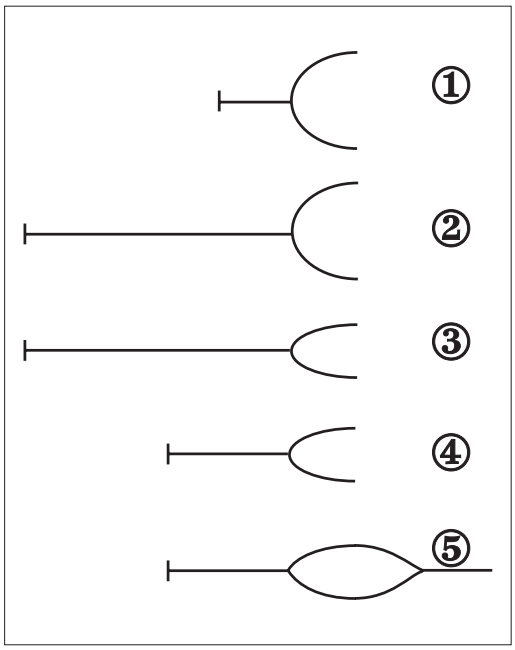

Figure 2.1. Schematic output

Let's assume that tracing 1 represents a normal tracing; therefore, if the patient is bleeding profusely in the presence of a fully functional clot, the reason most likely is surgical. Tracing 2 is the same as 1 as far as K, α, MA and LY30, but the R is elongated. However, tracing 2 is seldom seen clinically because of the interactive nature of hemostasis. If R is elongated, thrombin rate production is so slow that α, K, and MA will be affected. Keep in mind that thrombin, in addition to cleaving fibrinogen into fibrin, also is the most potent platelet activator on whose surface the enzymatic reaction occurs. Therefore, in the presence of such an elongated R, more often the resulting tracing will be similar to tracing 3. The elongated R has to be corrected first. Ten to fifteen minutes post-transfusion another sample is run to determine the effectiveness of the treatment and to further evaluate the resulting tracing.

In tracing 4, the R is slightly elongated but MA is very small. The slight elongation of R is due to the fact that platelets provide the surface where the enzymatic reaction takes place. Therefore, it appears likely that proper treatment such as platelets will normalize R as well as MA.

Similarly, in the case of tracing 5, a typical primary fibrinolysis pattern, where the R is slightly elongated and the MA is small and decreasing, fibrinolysis has to be treated before evaluating R, K, α , and MA, unless these parameters show hypercoagulability, where R and K are small, and MA and α large. In this case, the fibrinolysis is referred to as secondary fibrinlolysis, in that it is secondary to hypercoagulability, and an antifibrinolytic agent is contraindi-

cated, since, in these circumstances, fibrinolytic activations prevents microvascular fibrin deposit. In such cases, depending on the clinical situation, hypercoagulability may be treated with anticoagulant drug therapy.

TEG® Runs

There are two ways to run TEG® samples, depending on the number of columns available.

One is a "stepwise" approach (described in the previous section) where samples are run one after the other, in a specific order, to identify and treat stepwise the conditions encountered.

The other is a "simultaneous" approach where a number of samples are run at the same time:

1. With different reagents to enable the clinician simultaneously to evaluate and treat the parameters independently of each other, and/or
2. For differential diagnosis, a TEG® sample of untreated blood is superimposed or analytically compared to a blood sample treated in vitro with blood components, e.g., fresh frozen plasma, cryoprecipitate, platelets, or pharmacological agents, e.g., amicar or protamine sulfate. These tracings can easily differentiate in vitro which treated sample produces a normal tracing, and indicates which treatment will likely cause a similar effect in vivo[8,9].

Differential Diagnosis (Simultaneous Runs)

This section describes a strategy for performing differential diagnosis using the simultaneous samples technique and the TEG® Analytical Software to allow easy identification of therapy.

By adding blood components such as FFP or platelets, or pharmacological agents such as amicar or heparinase to patient blood samples, you can use the software to help you determine which treatment will be most effective.

Note that Chapter 4, "Looking at TEG® Data" begins the description of the use of the software in detail. The following description is meant only to illustrate the example.

For example, suppose that a patient sample produces a tracing as shown next:

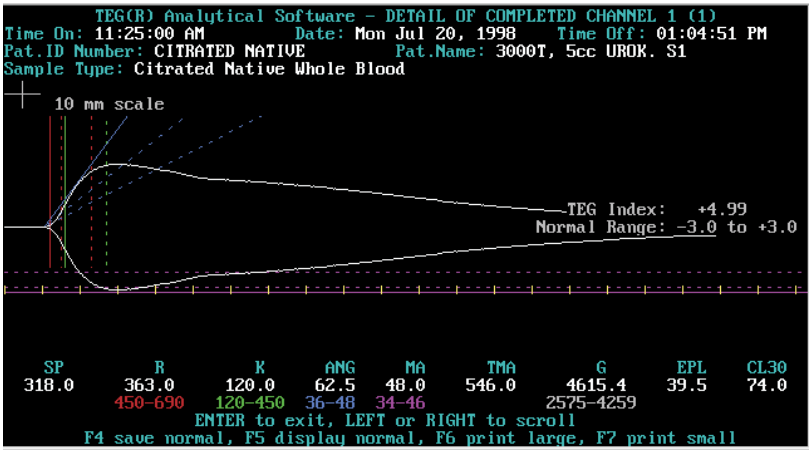

Figure 2.2. Untreated patient sample tracing

A qualitative inspection of this tracing, using the guidelines given earlier on page 14, invites a diagnosis of fibrinolysis. Earlier sections describe treatment with blood components or pharmacological agents under these conditions. Therefore, in vitro, you could run several samples, perhaps adding FFP to one sample, amicar to another, and platelets to still another. Suppose the amicar-treated sample produced the tracing shown in figure 2.3. This tracing appears to approach normal values.

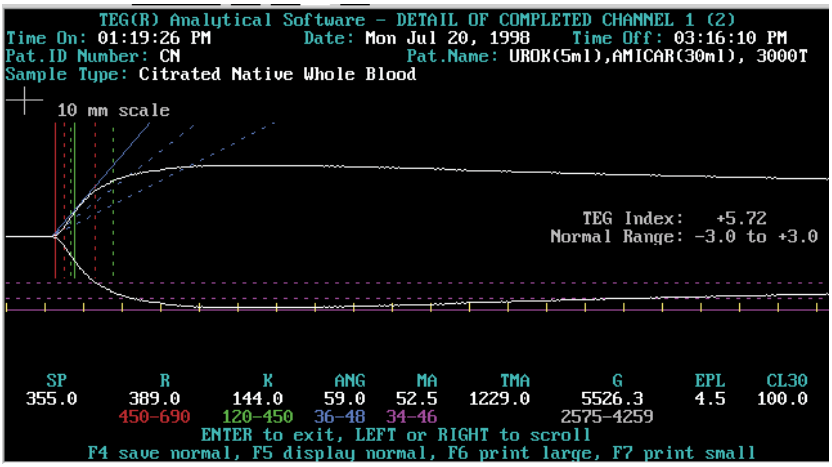

Figure 2.3. Patient sample treated with amicar

The TEG® Analytical Software can store normal tracings that can then be superimposed on patient tracings for comparison. If we superimpose the normal tracing on top of both the patient tracings shown in figures 2.2 and 2.3, we see the following result:

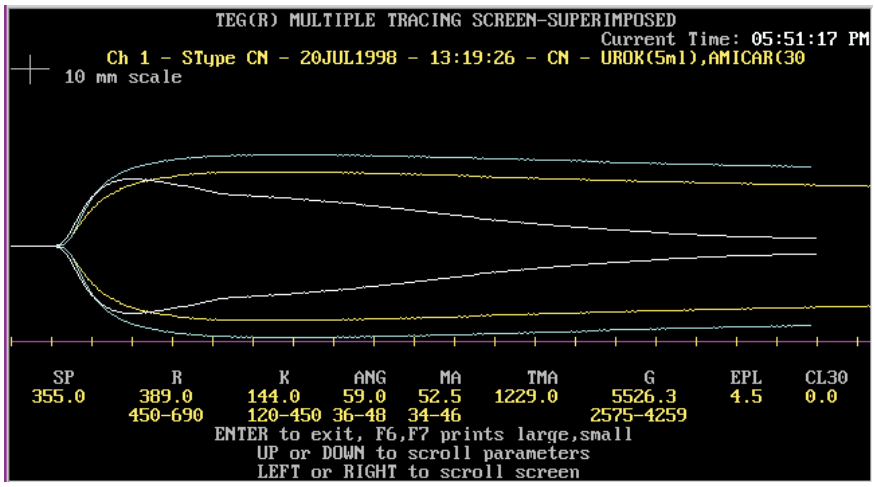

Figure 2.4. Normal tracing superimposed on patient tracings (outer tracing is normal tracing; middle tracing is amicar-treated patient sample; inner is untreated sample). Note that on the actual screen these tracings are differentiated by color.

You can see that the amicar-treated blood sample produces output that closely matches the normal values.

Tracing Analysis Exercises

Exercises in the analysis of TEG® tracings can be found on the Internet Journal of Anesthesia, which can be accessed from Haemoscope's web site at:

www.haemoscope.com/pubinet.html

or directly at:

www.ispub.com/journals/IJA/Vol1N3/teg.htm

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