

# Critical Factors Contributing to the Thromboelastography Trace

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## ABSTRACT

The thromboelastography trace provides a graphical and numerical representation of the viscoelastic changes associated with fibrin polymerization. When used with whole blood, the shape of this trace is a composite of the effects of white and red cell content and composition, platelet number and function, fibrinogen concentration, as well as coagulation protein function and balance. The trace is also influenced by pharmacological agents such as anticoagulants, antiplatelet therapy, and coagulation factor supplementation. As such the main role of this technology has been as a point-of-care device to guide transfusion of blood components. Recently the technology has moved from the cardiac and hepatic surgical settings, where most of the early work was focused, into other areas of hemostatic monitoring. New applications for pharmaceutical monitoring and patient screening are being explored. This review gives a broad overview of the applications of the technology. In particular it considers the factors that most influence the characteristics of the trace, be they preanalytical, analytical, or clinical.

**KEYWORDS:** Thromboelastography, thromboelastometry, hemostasis, global screening.

Thromboelastography was first described >60 years ago.<sup>1</sup> Since then, several variants have evolved. Several coagulation monitoring devices are now on the market that assess the viscoelastic properties of blood including the Thromboelastograph (TEG) (Haemoscope Corporation, Niles, IL), the ROTEM (Pentapharm GmbH, Munich, Germany), and the Sonoclot analyzer (Sienco Inc., Arvada, CO). They provide graphical representations of the dynamics of fibrin polymerization in citrated or noncitrated whole blood, platelet-rich or platelet-poor plasma, with or without activation. The process is displayed in real time and provides numerical data for such parameters as time to clot, rate of formation of the clot, strength of the clot, and stability of the clot along with assessment of fibri-

nolysis. To interpret viscoelastic hemostatic assays (VHAs), the components of the trace and the different terminology used need to be understood (Fig. 1).

These technologies employ a sample cup and a centrally placed pin/probe that form the reaction chamber. Fibrin polymerization is either detected by progressive restriction of the oscillation of the cup (TEG), a detector pin submerged in the reaction chamber (ROTEM), or restriction of the vertical oscillation of the probe (Sonoclot). This review concentrates on factors affecting the thromboelastograph/thromboelastogram trace produced by the TEG/ROTEM.

As with all tests of hemostasis, published data should be reviewed in light of the assay variant used and the stated normal range of the testing center. This

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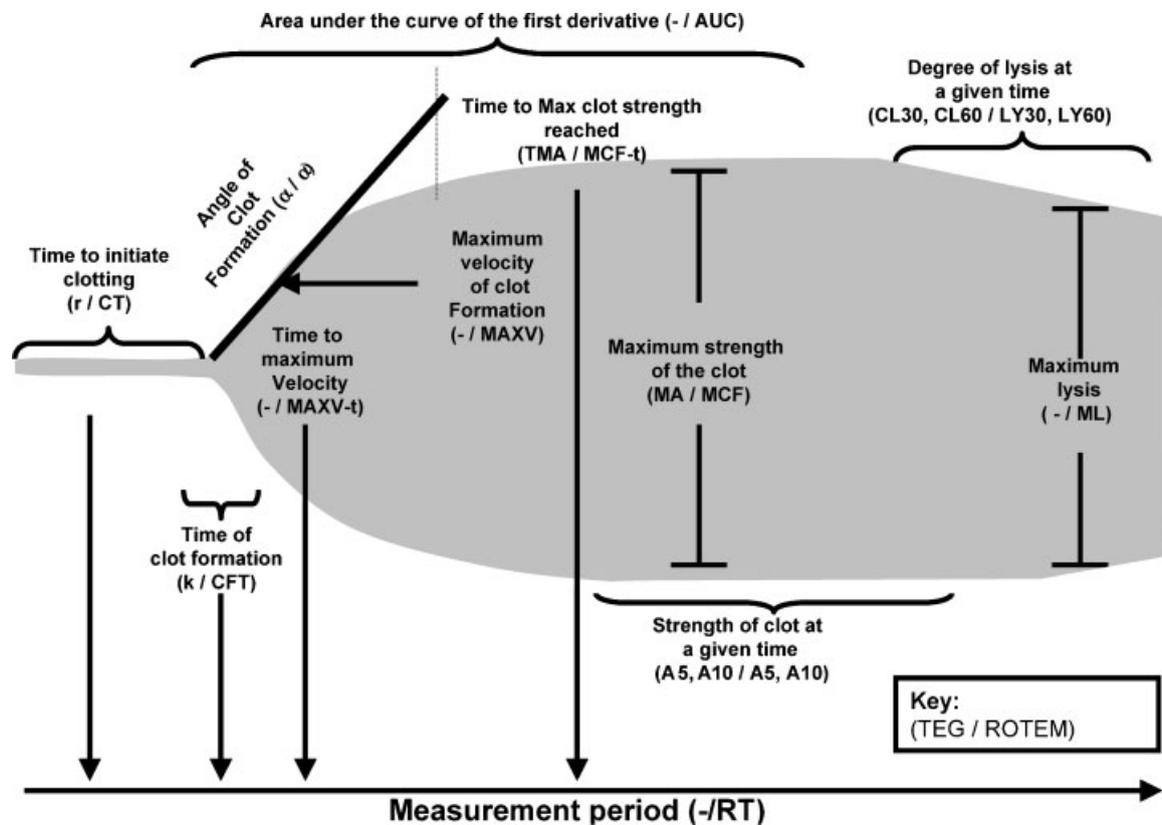
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**Figure 1** Viscoelastic hemostatic assays (VHA) terminology and parameters.  $\alpha$ , alpha angle; AUC, area under the curve; CFT, clot formation time; CL (t), clot lysis (at time t); CT, clot time; k, rate of clot formation; LY (t), lysis (at time t); MA, maximum amplitude; MAXV, maximum velocity; MAXV-t, time to maximum velocity; MCF, maximum clot firmness; MCF-t, time to maximum clot firmness; ML, maximum lysis; r, time to clot initiation; ROTEM, Rotational Thromboelastogram; RT, reaction time; TEG, Thromboelastograph; TMA, time to maximum amplitude; -, no equivalent parameter.

was highlighted by Nielsen<sup>2</sup> when the ROTEM and TEG were compared against manipulated blood samples. Nielsen described a shortened reaction time, increased reaction velocity, and increased clot strength in the ROTEM relative to the TEG. These differences were attenuated by the use of a contact activator, suggesting that differential contact activation in the native test systems may contribute to the differences. This highlights another consideration that published data must be related not only to the technology but also to the test configuration used, for example whether extrinsically or intrinsically activated and whether platelet or heparin inactivation was used. Again, as with other tests of hemostasis, when standardization is applied, good agreement in results can be seen between centers.<sup>3</sup>

A major limitation of VHAs is the wide range of normality. This appears inevitable as a test becomes more “global.” As whole blood analytical tools, VHAs are influenced by white and red cell content and composition, platelet number and function, fibrinogen concentration, as well as coagulation protein function and balance. Therefore it is more readily employed in the monitoring of change within an individual relative to a

“baseline” reading rather than a diagnostic “snapshot” related to a general reference range.

## PREANALYTICAL

Several preanalytical factors can affect the VHA trace (Fig. 2).

### Hematocrit

Hematocrit has been shown to influence the clot strength. In a study of 40 sideroblastic anemia patients, the maximum clot firmness (MCF) in the ROTEM showed an inverse correlation with hematocrit.<sup>4</sup> A corresponding increase in thrombin generation was not found. They demonstrated that this increase in MCF could be replicated in vitro by artificial manipulation of the hematocrit. This hypercoagulable trace seen in the ROTEM is therefore likely to be a function of the assay rather than an in vivo clinical observation. For this reason care must be taken when analyzing the ROTEM in patients with decreased hematocrit.<sup>4</sup> Hypercoagulability of the ROTEM with normal thrombin generation was reported in splenectomized thalassemia



An alternative to flushing out the heparin by means of discarded blood is the addition of heparinase to neutralize the heparin. A comparison of heparinase-treated blood versus untreated blood can be used to eliminate the heparin effect from background hemostatic potential in patients treated with heparin. This is often used in the hemostatic assessment of patients on cardiopulmonary bypass.

## ANALYTICAL

Basic analytical variances that were alluded to earlier will, despite correlation, give numerical differences that will affect the interpretation of results such as between TEG and ROTEM<sup>14</sup> and between activated and non-activated analysis. Originally VHA was performed using native whole blood allowed to clot without the use of additional reagents. Today several different reagents are used in VHA (summarized in Table 1).

### Normal Ranges

As highlighted earlier, the results of VHAs need to be interpreted carefully. Many methodological variations can affect the results, and knowing these technical limitations allows the test to be performed reproducibly.

Even when using the reagents and technology to the manufacturer's specifications, it is advisable to determine a local normal range and when testing citrated samples enforce a strict time post venipuncture for testing. A 2008 Canadian study compared a local population range with a manufacturer's recommendation. They found that 10 of 118 "normal healthy" volunteers would have been described as coagulopathic against the manufacturer's range.<sup>15</sup>

Age and sex also influence VHA. In an adult population, being female and advancing age both give a more hypercoagulable trace.<sup>3</sup> However, few centers describe specific ranges adjusted for age and sex.

**Table 1 Modifications of Viscoelastic Hemostatic Assays**

Modification	Application
Ellagic acid	Intrinsic activator
Kaolin	Intrinsic activator
Tissue factor	Extrinsic activator
Heparinase	Heparin neutralization
Antifibrinolytics	Eliminate fibrinolysis
Heparin	Thrombin inhibition
Arachidonic acid (AA)	Activates platelets via thromboxane A2 receptor
Adenosine diphosphate (ADP)	Activates platelets via ADP receptor
Glycoprotein IIb/IIIa inhibitors	Inhibits platelet aggregation
Cytochalasin D	Inhibits cytoskeletal assembly

There are significant differences in VHA values between neonates, children, and adults.<sup>16-19</sup> Edwards et al<sup>16</sup> reported comparative data between neonates, children, and adults using a nonactivated TEG. In their study, the neonatal reaction time was longer and rate of clot formation slower than for their children and adult populations. Results for the children (2 to 11 years of age) and adult groups were comparable. A significantly decreased MCF in cord blood in comparison with adults was reported in extrinsically activated ROTEM,<sup>14</sup> a finding shown to a lesser extent by Edwards et al.<sup>16</sup> Age-specific reference ranges for a kaolin-activated TEG for the age group 1 month to 16 years have been reported.<sup>17</sup> These publications can be used as a guide to expected values, but care should be taken when using the data presented because each group reported using different methodology.

### pH and Temperature

Other considerations are where the analysis is being performed in conditions at variance to the clinical situation. An example of this is in the acidotic or hypothermic patient. Here the laboratory conditions are not the same as those experienced by the patient, and VHA performed under different pH and/or temperature conditions give markedly different results.

In vitro acidification of whole blood has been reported to impair parameters of the TEG<sup>20</sup> including a significant delay in CT, impairment to clot formation rate, and clot strength. Alkalization of patient plasma did not show this effect. Hypothermia showed the same effects as acidification but to a lesser extent in the ROTEM<sup>21</sup> and TEG<sup>20</sup> but had a synergistic relationship with acidosis when both were present using the ROTEM system.<sup>22</sup> The results generated under standard conditions should be viewed as representing the hemostatic potential if the acidosis and/or hypothermia were corrected.

### Quality Assurance and Quality Control

External Quality Assurance (EQA) provides a medium whereby safety and performance is improved, accuracy and precision are determined, and variables contributing to this accuracy and precision can be audited. It is a requirement in the modern laboratory for accreditation and regulation by external bodies; however, as yet there is no widely used scheme whereby whole blood samples can be tested in an EQA setting for TEG/ROTEM.

Commercial controls are available for both normal and abnormal samples and provide the means whereby daily assessment of quality control is available. This allows the operator to assess aspects of the assay including machine function, operator competency, and

quality of reagents. This topic is covered in greater depth elsewhere in this issue.<sup>23</sup>

**CLINICAL**

**Therapeutic**

**BLOOD COMPONENT THERAPY**

The use of TEG/ROTEM to guide blood component replacement therapy has been one of the main point-of-care uses for these devices. Essentially, an increased clotting time is associated with the need for plasma component replacement, whereas decreased clot strength is associated with the need for either platelet transfusion or fibrinogen supplementation (Fig. 3). The influence of these two factors on the clot strength can be dissected by studying the results in the presence and absence of platelet inhibitors (Table 1).

Two major surgical specialties have the most experience in TEG/ROTEM-guided replacement therapy: hepatic surgery and cardiac surgery. TEG has been used >20 years to guide blood component therapy during liver transplantation,<sup>24</sup> but the lack of guidelines and clearly defined thresholds for component administration have left concerns about the clinical use of algorithm-based replacement therapy in hepatic surgery.<sup>25</sup> Equally, transfusion practice is likely to differ depending on the protocol used for the viscoelastic analysis.<sup>26</sup>

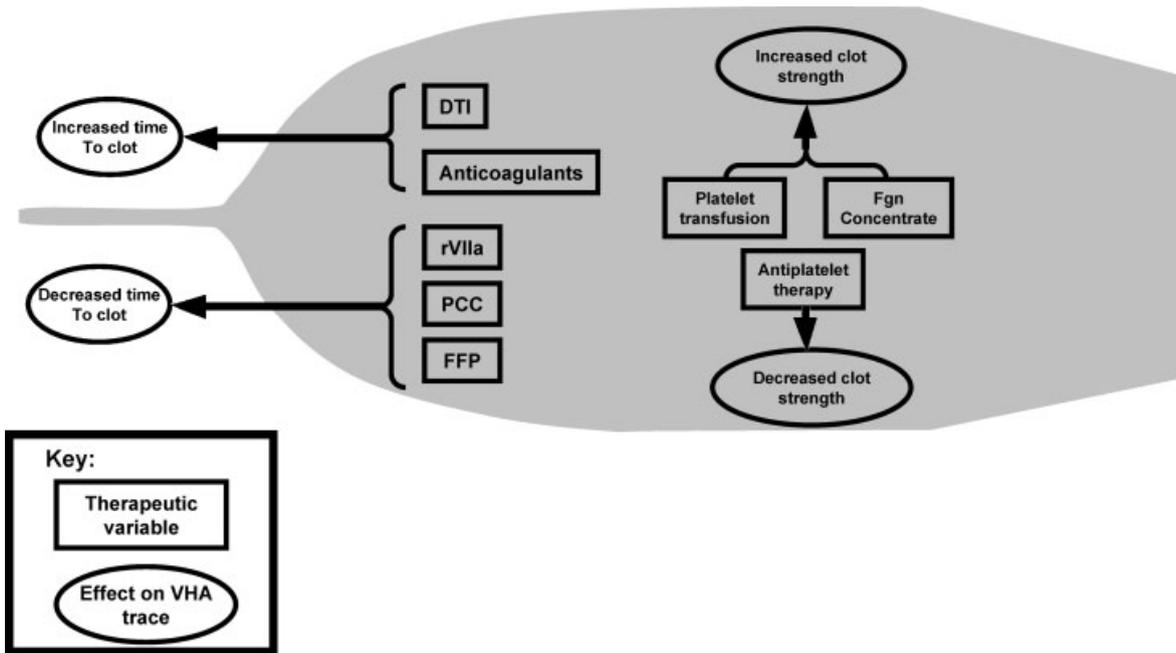
Cardiothoracic surgery uses 5% of all donated blood in the United Kingdom and 10% of blood in the United States.<sup>27</sup> The use of TEG-based algorithms for

blood component use in cardiac surgery is well established and has better defined guidelines than seen in hepatic surgery. The recent guidelines on antiplatelet and anticoagulant management in cardiac surgery gave a grade B recommendation that TEG may be used to guide transfusion in the postoperative period.<sup>27</sup> Two randomized controlled trials have been performed that demonstrated reduced component therapy use when a TEG-based decision-making algorithm was used without clinical detriment.<sup>28,29</sup> However, in both studies the TEG allowed earlier intervention that may have resulted in better efficacy of the products.

**ANTIPLATELET DRUG RESISTANCE**

The number of percutaneous coronary interventions has exploded over the past 15 years. A major complication in these procedures is acute vessel or stent occlusion. Therefore, many therapeutic strategies have been employed to inhibit platelet aggregation/activation in an attempt to limit this catastrophic event occurring. Despite this, a significant number of patients appear resistant to therapy and are thus at high risk of occlusive complications.<sup>30</sup> VHA has been found to have a clinical use in the monitoring of antiplatelet medication. The clot strength as measured by VHA is composed of a contribution from both fibrin and platelet elements. The platelet component of VHA traces can be drawn out through the use of specific platelet agonists added to the reaction mixture (Table 2).

The use of adenosine diphosphate (ADP) as a platelet activator enables the detection of ADP receptor-inhibiting drugs such as clopidogrel. Similarly, the



**Figure 3** Therapeutic variables affecting the viscoelastic hemostatic assay (VHA) trace. DTI, direct thrombin inhibitors; FFP, fresh-frozen plasma; Fgn, fibrinogen; PCC, prothrombin complex concentrates; rVIIa, recombinant activated factor VII.

**Table 2 Platelet Mapping by Viscoelastic Hemostatic Assay**

	Platelet Mapping			
	Cup 1	Cup 2	Cup 3	Cup 4
Activator	Intrinsic activator	Heparin	Heparin	Heparin
		Reptilase	Reptilase	Reptilase
		Factor XIIIa	Factor XIIIa	Factor XIIIa
		Adenosine diphosphate	Arachidonic Acid	
Contribution to clot strength	Fibrin and platelet Thrombin activation	Fibrin only	Fibrin	Fibrin
			Platelet via adenosine diphosphate receptor	Platelet via thromboxane A <sub>2</sub> receptor

use of arachidonic acid (AA) as a platelet activator allows the detection of AA-inhibiting drugs such as aspirin. The main application of this "platelet mapping" is in cardiac patients where it is used to identify patients who are resistant to platelet-inhibiting drugs.

There are many bedside options for the assessment of antiplatelet drug resistance other than VHA, such as PFA-100 (Dade Behring, Deerfield, IL) that was recently released with a clopidogrel-sensitive cartridge,<sup>31</sup> VerifyNow (Accumetrics, San Diego, CA, USA), Platelet works (Helena Laboratories, Allen Park, MI), and Multiplate (Dynabyte Medical, Munich, Germany).

#### REPLACEMENT THERAPY IN HEMOPHILIA

The management of hemophilia is very well described using conventional coagulation assays. However, it is increasingly realized that response to treatment differs among individuals. Furthermore, the clinical course of the disorder is different among individuals with the same severity of disease as assigned by factor VIII:C value. Attention has turned to global assays of hemostasis such as assays based on thrombin generation or fibrin polymerization. Thromboelastography has thrown up some differences compared with traditional assays.<sup>32</sup> Looking at patients with factor VIII levels of 0.01 to 0.05 IU/mL, some behave thromboelastographically like a severe form (i.e., <0.01IU/mL), whereas others give a normal-looking trace. Likewise the TEG traces of some patients with severe hemophilia were normalized by the addition of 0.05 IU/mL of factor VIII, whereas others required 10 times this quantity.<sup>32</sup> Unfortunately, no clinical correlations have been reported for these TEG findings.

Correlation is poor between TEG and factor VIII levels. Although TEG is able to differentiate patients with severe and moderate hemophilia from normal patients, it has been shown to be less sensitive than thrombin generation assays.<sup>33</sup> Although the plasma one-stage assay shows a linear relationship between FVIII level and dose administered, this is not seen in the whole blood VHA. A 30% increase in plasma FVIII contributes to a 90% increase in ex vivo hemostatic effect measured by the MCF. This indicates

there is more of a hemostatic effect than purely that caused by increasing plasma FVIII concentration. This suggests that the hemostatic effect of supplementing factor VIII is not purely a plasma event but involves cellular interplay.<sup>34</sup>

A challenge in hemophilia care is the treatment of patients with coagulation factor-specific inhibitors. The use of pharmacological agents such as recombinant activated factor VII (rFVIIa) cannot easily be monitored using the prothrombin time (PT) and activated partial thromboplastin time (aPTT),<sup>35</sup> and factor assay levels are not as clinically useful as in noninhibitor patients.<sup>36</sup> Using tissue factor (TF)-activated TEG/ROTEM, administration of rFVIIa to acquired hemophilia A patients resulted in correction of their coagulation profile from the previously hypocoagulable trace. VHA traces, if sufficiently abnormal to begin with, can be useful in monitoring treatment but only in individual patients.<sup>37,38</sup>

In hemophilia management, TEG has been shown to reflect the clinical efficacy of activated prothrombin complex concentrates and rFVIIa<sup>39</sup> (Fig. 3). Sørensen and Ingerslev<sup>39</sup> reported an algorithm for preoperative assessment of patients with hemophilia. They suggested that a PT, aPTT, platelet count, fibrinogen, factor VIII level, and inhibitor screen be undertaken along with ex vivo evaluation and dose titration of activated prothrombin complex concentrates and rFVIIa using whole blood thromboelastography.<sup>39</sup> Another group have suggested a role of VHA in the differentiation of the effectiveness of different FVIII preparations in a given patient. A disulphide bond stabilized B domain-depleted FVIII appeared to have greater influence on clot formation rate, times, and clot firmness values than other preparations.<sup>40</sup> This may provide a valuable insight into the effectiveness of different treatments in individual patients.

#### FIBRINOGEN

The use of fibrinogen concentrates has largely been restricted to the treatment of congenital fibrinogen deficiency. Over the past 2 years there have been several reports of the successful use of fibrinogen concentrates to

treat acquired fibrinogen deficiency. Many of these have used a platelet-inhibited VHA as a means of monitoring the fibrinogen administration.<sup>41,42</sup> This modification of VHA can be used to monitor fibrinogen independently of platelet count.<sup>43</sup> In most cases the requirement for autologous blood transfusion has been reduced. If the current trend for wider use of fibrinogen concentrates continues, we may see more use of VHA monitoring in these cases.

#### HEPARIN MONITORING

Therapeutic unfractionated, low molecular weight heparins (LMWHs) and danaparoid show a dose-dependent affect on TEG parameters at lower concentrations than will affect the PT, aPTT, and thrombin time<sup>44</sup> and activated clotting time.<sup>45</sup> The aPTT is only slightly prolonged at doses of heparin that will completely inhibit TEG clotting. The anti-Xa assay is more sensitive than the standard TEG for LMWH monitoring. By comparing the heparinase modified TEG with the standard TEG, the difference between 0.005 and 0.05U/mL of unfractionated heparin can be detected to a greater sensitivity than the anti-Xa activity assay.<sup>46</sup> The anti-Xa assay was more sensitive than the TEG when LMWH or danaparoid were assessed.<sup>46</sup> The degree of inhibition of TEG parameters does not necessarily correlate with plasma levels of the drug,<sup>44</sup> although it can have predictive utility for recurrence in deep vein thrombosis patients receiving LMWH.<sup>47</sup>

#### OTHER DRUGS

The next generation of anticoagulants offers a challenge to the laboratory in terms of monitoring effect. The global nature of VHA assessment may provide a means of assessment. A recent study described a potential role of ROTEM in patients with heparin-induced thrombocytopenia treated with the direct thrombin inhibitor Argatroban.<sup>48</sup> They found a strong and highly significant

correlation ( $p < 0.0001$ ) between Argatroban concentration and CT and time to maximum velocity within the therapeutic range of Argatroban. Similarly bivalirudin has been shown to prolong  $r$  in the TEG and could offer a means of monitoring this drug in similar situations.<sup>49</sup>

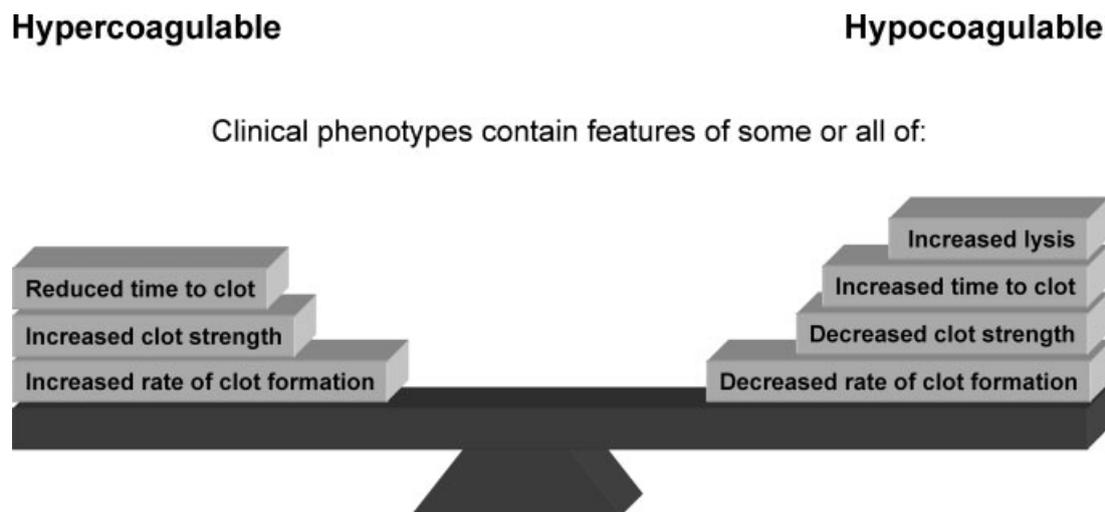
#### Pathological

When assessing pathologies by VHA, the clinician wants to know whether his or her patient has a higher risk of bleeding (hypocoagulable) or an elevated risk of thrombosis (hypercoagulable) compared with a normal individual (Fig. 4). VHA can also offer some prognostic value in combination with other tests.

#### HEPATOLOGY

Recently VHA has been used to try and assess hemostasis in patients with liver impairment outside of the operating room. The coagulopathy of hepatic dysfunction is multifactorial, involving coagulation, fibrinolysis, and platelet function. Because VHA is potentially affected by all of these interactions, it would appear to offer advantages over standard laboratory tests such as the PT, aPTT, and platelet count. The PT is used as an indicator of hypocoagulability, but recently standardization issues of PT measurement between centers have raised questions about the use of this test, particularly as a component of severity indexes such as the Model for End-Stage Liver Disease score.<sup>50</sup> Hypercoagulability is also a problem associated with liver disease and has been demonstrated using the TEG in live liver donors<sup>51</sup> and in extrahepatic portal vein thrombosis and noncirrhotic portal fibrosis.<sup>52</sup> Hypercoagulability was judged by an increase in the clot index ( $CI = 0.3258 r - 0.1886 k + 0.1224 MA + 0.0759 \alpha - 7.7922$ ), a formula that takes into account several TEG parameters.

Hyperfibrinolysis, shown by a rapid breakdown of the clot, is one of the more marked abnormalities



**Figure 4** Changes in the viscoelastic hemostatic assay trace in the presence of pathologies.

visualized used VHA. It tends to occur late in the anhepatic phase of liver transplantation and is most noticeable during organ reperfusion.<sup>53,54</sup>

The ROTEM has been shown to be suitable for the assessment of stable cirrhotic patients. The CFT and MCF were shown to differentiate patients from normal volunteers, and both were correlated with platelet count, fibrinogen, and antithrombin.<sup>55</sup>

The presence of heparinoids (glycosaminoglycans) further complicates the hemostatic picture in cirrhotic patients. Levels of these heparinoids are particularly raised in acute liver failure and at reperfusion of donor organs during liver transplantation. Both of these situations are associated with gross changes to many of the VHA parameters. The degree of abnormality that can be attributable to this heparin-like effect was demonstrated using TEG with and without heparin neutralization.<sup>56</sup>

### CARDIOLOGY

An abnormal TEG has been suggested as a predictor of patients who will bleed during cardiac surgery,<sup>57</sup> but others have disputed this finding.<sup>58,59</sup> Others have suggested that VHA may be better used as a negative predictor of hemostatic blood loss rather than as a positive predictor.<sup>60,61</sup> The major uses of VHA in cardiology are in the monitoring of blood component therapy and assessment of antiplatelet effects. Both of these are discussed elsewhere in this review.

### THROMBOEMBOLIC EVENTS

Dai et al<sup>62</sup> recently reviewed the literature regarding postoperative thrombosis prediction. They identified 10 studies covering 1056 patients. Most of the studies used the TEG and reported favorable results supporting the TEG's prediction of thromboembolism. However, there was no consensus definition of hypercoagulability. Although the clot strength was probably the best parameter for identifying hypercoagulability, there was no consensus on an appropriate cut-off value for diagnosis of thromboembolic events. Within the studies reviewed, sampling criteria and assay standardization were poorly defined.<sup>62</sup> Using data from the largest study included in the review,<sup>63</sup> if the postoperative pretest probability of a thromboembolic event was 4%, a positive TEG would raise this to 8%, and conversely, a negative TEG<sup>®</sup> would decrease this to 1%. In higher risk patients, a pretest probability of 45% would rise to 63% with a positive TEG and fall to 21% in the presence of a negative TEG. The conclusion of the review was that the predictive accuracy of TEG for postoperative thromboembolism was very variable and that a high-quality diagnostic study examining VHA as a predictive tool was required to define clinical utility.

Simultaneous pancreas and kidney transplantation has long been associated with thrombotic compli-

cations. A hypercoagulable state (shortened CT, increased rate of clot formation, and enhanced clot strength) can be seen in these patients, and TEG is often used pre-, intra- and postoperatively to guide the use of anticoagulation.<sup>64</sup>

### OBSTETRIC AND NEONATES

A hypercoagulable state develops during pregnancy, presumably as a defense mechanism against hemorrhage. The increase in coagulation proteins is thought to be due to the influence of estroprogestative hormones. This state slowly resolves during the first month postpartum.<sup>65</sup>

Thromboelastographic changes may indicate pregnancy-related problems, but clinical use of these findings is limited because the changes seen are often within the normal ranges for the normal pregnancy.

Assessment of hemostasis in neonates is complicated by the lack of "normal" ranges, which, for ethical reasons, are not practical to assign at each hospital. Neonatal hemostasis often appears hypocoagulable when compared with existing adult ranges. A more detailed review of the use of VHAs in obstetrics was recently published.<sup>66</sup>

### TRAUMA

A detailed review of trauma-associated VHA changes is beyond the scope of this review; see Gonzalez et al and Johansson et al<sup>67,68</sup> for more information. As described in the obstetric section of this review, VHA is very good at monitoring changes within an individual case. However, diagnosing a primary defect is more difficult because the changes seen can often fall within the reference range.<sup>69</sup>

Trauma coagulopathy is often exacerbated by hypothermia and acidosis. By assessing VHA under hypothermic and acidotic conditions, it is clear that hypothermia produced a hypocoagulable VHA trace (increased CT, decreased rate of clot formation, and decreased clot strength) that was synergistically impaired by acidosis.<sup>21,22</sup> Therefore, the determination of VHA under pathological rather than laboratory conditions may add to the clinical picture in trauma assessment.

### CONGENITAL PLATELET DYSFUNCTION

The TEG/ROTEM has not yet been shown to be a useful tool for the diagnosis of congenital platelet disorders. An example of this is a description of Glanzmann's thrombasthenia patients where clear clinical improvement was seen with little variance in ROTEM parameters.<sup>70</sup>

### CONCLUSION

VHA has been used for many years to monitor blood replacement therapy in cardiac and hepatic surgery.

Recently, renewed interest has led to the application of this technology in many other areas of hemostasis. As the technology diversifies with different machinery, reagents, and applications, it is important to understand these differences when interpreting any data generated. Therefore, all centers that use VHA should be aware of the detail of the technique they are using and importantly be aware of the limitations of that technique. When comparing published data, it is also important to know and understand the variants of the assays used.

This is an exciting time for the application of global assays of hemostasis, and the assessment of the viscoelastic properties of fibrin polymerization is an important tool in the development of these new approaches.

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