

## CRITICAL REVIEW

# Clinical utility of viscoelastic testing (TEG and ROTEM analyzers) in the management of old and new therapies for hemophilia

Sarah Ramiz<sup>1</sup> | Jan Hartmann<sup>2</sup>  | Guy Young<sup>3</sup> | Miguel A. Escobar<sup>4</sup> | Meera Chitlur<sup>1</sup>

<sup>1</sup>Wayne State University School of Medicine, Children's Hospital of Michigan, Detroit, Michigan

<sup>2</sup>Haemonetics Corporation, Braintree, Massachusetts

<sup>3</sup>University of Southern California Keck School of Medicine, Children's Hospital Los Angeles, Los Angeles, California

<sup>4</sup>University of Texas Health Science Center and the McGovern Medical School, Houston, Texas

### Correspondence

Meera Chitlur, Barnhart-Lusher Hemostasis Research Endowed Chair, Director, Hemophilia Treatment Center and Hemostasis Program & Special Coagulation Laboratory, Professor of Pediatrics, Wayne State University School of Medicine, Division of Hematology/Oncology Children's Hospital of Michigan, Detroit, MI.  
Email: mchitlur@med.wayne.edu

### Abstract

Hemophilia A and B are rare inherited bleeding disorders resulting from deficiency of coagulation factors VIII and IX respectively. In the past few decades, the field of hemophilia has witnessed pivotal management challenges and therapeutic advances. Routine coagulation and factor assays, while useful in the classification of severity and treatment monitoring in hemophilia patients, have been shown to be of limited use in managing clinical presentations and outcomes. This prompted the investigation of viscoelastic studies in hemophilia care, which have established their utility in various bleeding and thrombotic states. In this review, we will discuss and critically assess the current literature highlighting the use of viscoelastic studies in various aspects of hemophilia including the determination of clinical phenotype, management of patients with inhibitors, perioperative management, and monitoring of novel agents.

## 1 | INTRODUCTION

Thromboelastography was first described over half a century ago by Hartert.<sup>1</sup> Ever since, it has evolved from predominantly research use to wide clinical applications. As a global coagulation assay, thromboelastography provides a continuous assessment of clot formation and lysis, via the measurement of viscoelastic properties of whole blood under the effect of constant rotational force.<sup>2-4</sup>

Two modern technologies have adapted Hartert's principle; the TEG device manufactured by Haemonetics Corporation (Braintree, Massachusetts) and the ROTEM device distributed by Instrumentation Laboratory (Bedford, Massachusetts). Both instruments (TEG 5000 and ROTEM delta) consist of a sample cup, into which a pin is suspended that is connected to a torsion wire. The torsion wire is in turn monitored for movement. Ultimately, a graphical tracing is resulted in real time, depicting clot initiation, propagation, stabilization and clot lysis.<sup>2-4</sup> Results obtained with the TEG technology are often referred to as thromboelastography, while results from the ROTEM

based technology are described as thromboelastometry. Overall, the parameters generated from both instruments are considered comparable albeit not directly interchangeable.

Thromboelastography can measure the coagulation pattern in the sample either by relying primarily on contact activation with the cup (called native TEG) or as is done more commonly, where coagulation is accelerated utilizing intrinsic or extrinsic pathway activators which allows for transportation of the specimen to a lab and thereby increase utility and reliability of the assay. Commercial reagents are available through the manufacturing companies. For the TEG, kaolin coated vials are provided for intrinsic pathway activation, while for the ROTEM, the manufacturer provides reagents for both intrinsic activation (INTEM [partial thromboplastin phospholipid from rabbit brain]) and extrinsic activation (EXTEM [thromboplastin/recombinant tissue factor (TF)]). Investigators have utilized recombinant human TF (mostly Innovin; Siemens Healthcare Diagnostics, Erlangen, Germany) for extrinsic activation with TEG at different dilutions in an improvised fashion. This has been a source of controversy, as TF-mediated

extrinsic pathway activation is considered by some to be the more physiologic route but its' use has been complicated by several factors including the significant variability among different sources of TF, the lot-to-lot variability of TF given its biologic nature, the need to dilute the TF reagent several logs with the TEG technology, further increasing the variability, and finally the question regarding the need for contact system inhibition using corn trypsin inhibitor (CTI) when employing minimal concentrations of TF (<1 pmol), which itself is associated with few limitations including financial cost.<sup>2,5,6</sup> Consequently, the Scientific and Standardization Committee (SSC) of ISTH has recommended utilizing intrinsic pathway activation with kaolin (TEG) or INTEM (ROTEM) for routine clinical use awaiting further validation of extrinsic pathway activators.<sup>7</sup>

As a whole blood assay, viscoelastic testing is believed to account for the integral role of the cellular and acellular elements in clot formation that is, platelets, red blood cells, leukocytes and enzymatic factors of coagulation. The low shear forces utilized in these instruments are comparable to those of the venous circulation.<sup>2,3,7</sup> Viscoelastic testing can be performed at the point of care, providing results in real-time. As a result, it has become an integral tool in hemostatic monitoring and transfusion management in cardiovascular surgery, liver transplant and trauma and critical care surgery, among others.<sup>8-10</sup> Over the past 2 decades, viscoelastic assays have been studied in the diagnosis and management of inherited and acquired bleeding disorders, including hemophilia.<sup>2,7</sup>

Hemophilia A and B result from the deficiency of coagulation factors VIII and IX, respectively. Clinical severity is divided according to factor level into severe (FVIII < 1%), moderate (FVIII 1%-5%), and mild (FVIII >5%). Patients with severe hemophilia tend to suffer from debilitating spontaneous joint or muscle hemorrhages, while patients with mild deficiency are mostly at risk of posttraumatic and postsurgical bleeding.

Conventional coagulation and factor assays have been routinely used in the diagnosis and management of hemophilia, but have been found to have several limitations. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) lack platelets and only reflect the initiation of coagulation. For example, the aPTT measures the time to initiation of clot formation where only 5% of total thrombin has been generated. Neither assay provides information regarding the rate and strength of clot formation, nor lysis. In addition, both assays can be prolonged by other interfering proteins. Furthermore, It has been demonstrated that the aPTT based FVIII:C assay does not necessarily correlate with clinical severity.<sup>11,12</sup> Such limitations and the emergent needs in the care of hemophilia patients, such as monitoring bypassing

agent therapy in inhibitor patients where routine assays cannot be used, have triggered the search for new ways to assess the coagulation status in hemophilia patients. Thus, global assays including thromboelastography have been studied to complement routine assays in confronting challenges in hemophilia care.

This review summarizes and critically discusses the significance and current use of viscoelastic testing for the most relevant aspects of hemophilia care.

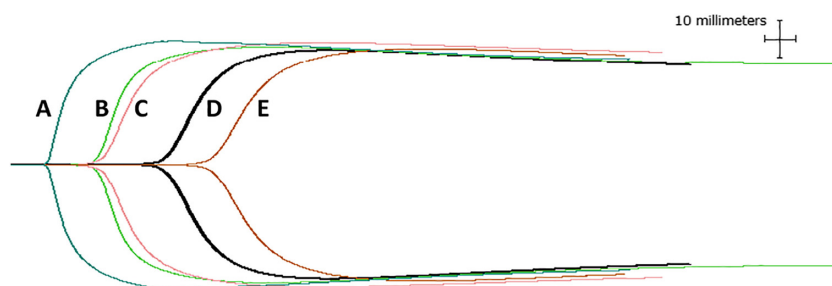
## 2 | PHENOTYPE HETEROGENEITY OF HEMOPHILIA

A considerable heterogeneity in clinical phenotype is recognized among patients with hemophilia. An estimated 10%-15% of patients with severe hemophilia A demonstrate a mild clinical phenotype, and conversely, patients with mild hemophilia may exhibit severe hemorrhagic manifestations.<sup>11,12</sup> FVIII:C and related aPTT although useful for the classification and management guidance in hemophilia, do not consistently correlate with the clinical phenotype.

Viscoelastic testing has been shown to help differentiate the clinical phenotype in such patients. The pioneering work of Sorensen et al. demonstrated variations in whole blood coagulation pattern in patients with hemophilia and other rare coagulation disorders utilizing thromboelastometry with minimal TF activation. This variation was evident on the routine parameters including clotting time (CT) and maximal clot firmness.<sup>12</sup> Furthermore, inter-individual variation was shown in response to ex vivo addition of rFVIIa, indicating the potential clinical role of thromboelastometry in dose titration of rFVIIa. Another report by Chitlur et al.<sup>13</sup> demonstrated that patients with a mild phenotype and no target joints had better clot formation and higher thrombin generation (MTG) on TEG 5000 compared with those with a more severe phenotype and presence of target joints.

Figure 1 depicts TEG tracings of patients with severe hemophilia A and FVIII:C < 1%, with clear differences in coagulation patterns, with those with milder phenotype showing earlier (shorter R time) and better clot formation (steeper angle). Thus, TEG technology can be considered a valuable method for better understanding of hemostasis and bleeding phenotype, and consequently tailoring individualized prophylaxis regimens.

Another aspect of phenotype determination is the differentiation between severe hemophilia patients with and without inhibitors, where the factor assay is inadequate for level detection below 1%.



**FIGURE 1** Superimposed TEG 5000 tracings in 4 patients with severe hemophilia A (FVIII <1%) (B-E) compared with normal control (A). Tracings to the left demonstrate superior coagulation pattern with shorter R time, steeper angle and larger maximum amplitude (MA) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Patients with severe hemophilia (factor level < 1%) are anticipated to have unmeasurable residual factor activity, whereas the presence of neutralizing antibody in inhibitor patients theoretically eliminates any residual activity. Salinas et al.<sup>14</sup> demonstrated the ability of kaolin-activated thromboelastography to distinguish between severe hemophilia A with and without inhibitors, where noninhibitor patients were shown to have shorter reaction and kinetics time. TF activated TEG and TGA, both with and without CTI, on the other hand were not able to distinguish patients with and without inhibitors, and none of the assays correlated with the annualized bleeding rates in these patients.

While such reports have laid the ground work for the wider use of thromboelastography in hemophilia, other reports have been contradictory. Tarandovskiy et al.<sup>15</sup> have studied different global assays in hemophilia, and have not found a difference in R time, angle or maximum amplitude when comparing TEG in severe hemophilia A patients with severe and mild phenotypes. It is unclear whether this is the result of assay discrepancy, reagent sensitivity or other modifiers of coagulation in the patient population. In other studies, TEG in mild hemophilia A has not been found to be sensitive enough to distinguish mild hemophilia A from normal controls and did not correlate with bleeding phenotype.<sup>16,17</sup> Bowyer et al.<sup>16</sup> also reported the lack of correlation of ROTEM parameters in 14 patients with mild hemophilia A and discrepant 1 stage and chromogenic FVIII levels.

### 3 | MONITORING OF ROUTINE FVIII PROPHYLAXIS

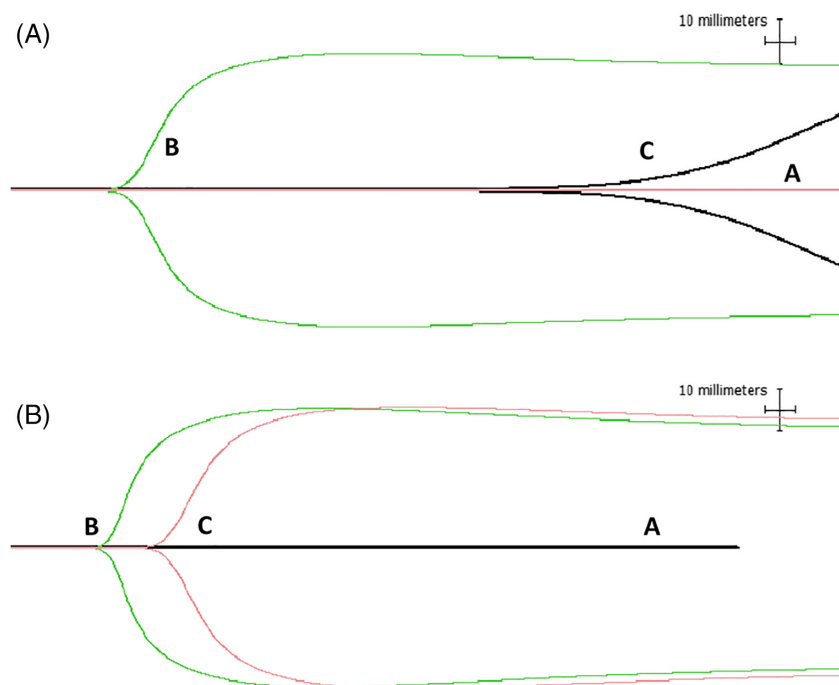
Patient care in hemophilia is becoming increasingly individualized. With the availability of newer factor products with half-life extension,

prophylaxis regimens are being tailored to allow patients to pursue sports and other activities. Given wide inter-patient variability in response to routine FVIII prophylaxis, pharmacokinetic (PK), and pharmacodynamic studies are thought to be essential for formulation of individualized treatment plans.

Thromboelastography can complement conventionally used plasma based FVIII assays. Al Hawaj et al.<sup>18</sup> correlated R time on TEG analyzer tracings with aPTT and FVIII activity during a 48-hour period of rFVIII prophylaxis in 8 severe hemophilia A patients with various bleeding phenotypes. At 48 hours, thromboelastography lost sensitivity similar to the undetectable level of FVIII activity. This implies that, having a POC PK result from thromboelastography may allow alterations in the prophylaxis regimen to be made in a timelier manner. Anecdotally at our center, visual thromboelastography read-outs with the time to clot have been found to be a very useful tool, to encourage and ensure patient compliance with prophylaxis. TEG tracings for 2 patients with severe hemophilia A and variable half-life response to FVIII supplementation are shown in Figure 2. Patient (1) demonstrates minimal coagulation pattern at 48 hours postFVIII infusion, necessitating a more frequent prophylaxis regimen. In contrast to patient (2), where sufficient coagulation is evident at 48 hours postinfusion thus requiring a less frequent infusion schedule.

### 4 | RESPONSE TO BYPASSING AGENTS

Bypassing agents, such as recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC), are successful in controlling bleeding episodes in inhibitor patients in approximately 80%-90% of cases. Nevertheless they are not as effective as



**FIGURE 2** (A) TEG 5000 tracing in patient 1 (severe hemophilia A) with short FVIII half-life. (B) TEG 5000 tracing in patient 2 (severe hemophilia A) with long FVIII half-life. Prefactor supplementation is shown in tracing (A) as a flat line with absent clot initiation, and 24-hour postfactor supplementation is shown in tracing (B) with significant improvement of clot initiation and amplification in both patients 1 and 2. 48-hour postfactor supplementation is shown in tracing (C) with near return of thromboelastography parameters to baseline in patient 1, compared to patient 2 where residual clot formation is seen [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

native FVIII or FIX products.<sup>19–21</sup> When using bypassing agents, routine assessment of factor levels or aPTT/PT are no longer an option for monitoring therapy and other parameters to guide the choice of bypassing agent, optimum dosing and monitoring of response to therapy are needed.

Viscoelastic testing may provide useful information to guide the use of bypassing agents; occasionally patients demonstrate clinical responsiveness to either aPCC or rFVIIa, and thromboelastography has been used to determine the agent to which the patient shows better response.<sup>22,23</sup> Such information is particularly valuable in the setting of uncontrolled bleeding or perioperative planning in patients with inhibitors. Young et al. used thromboelastography in the formulation of an effective individualized treatment plan in challenging inhibitor patients. TEG technology was noted to be useful in demonstrating response and half-life assessment of rFVIIa and FEIBA infusions separately or in combination leading to improved control of bleeding episodes while decreasing number of infusions and hospitalization days.<sup>24</sup>

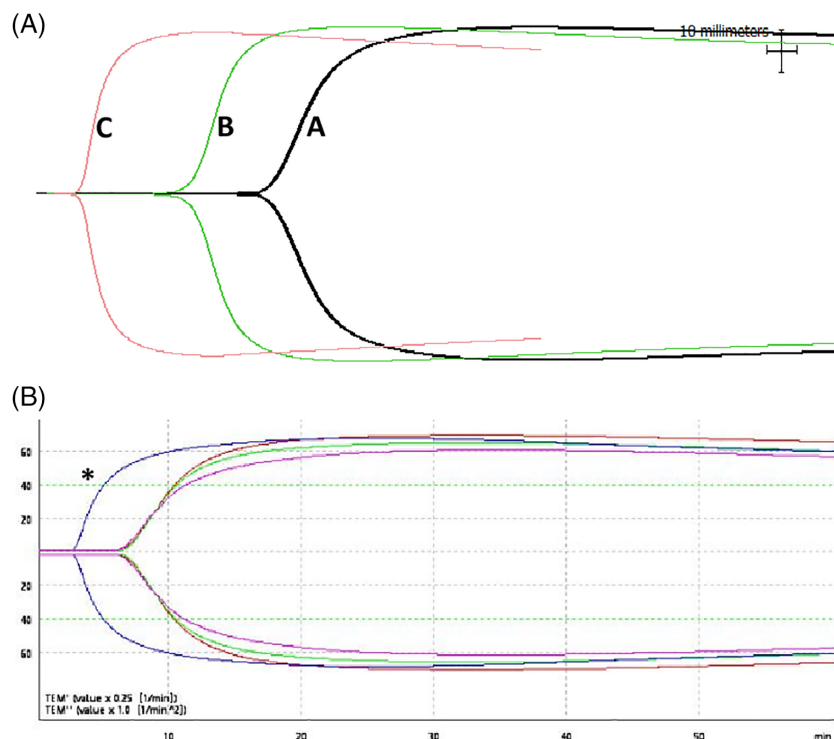
Figure 3A is an example of how thromboelastography was used in a patient with severe hemophilia A with high-titer inhibitors, who failed immune tolerance induction three times. He was maintained on treatment with rFVIIa for management of bleeding with good response, but presented with a hip joint bleed not responding to rFVII over several days. Faced with hesitation to use plasma derived aPCC, thromboelastography was utilized, which showed superior response to aPCC compared with rFVIIa, and was subsequently given for

treatment with excellent response. Without the availability of viscoelastic testing, treatment is primarily empiric and responsive, based on monitoring of clinical presentation.

While rFVIIa is conventionally used in repeated doses (90 mcg/kg for 3 doses), the single high dose regimen of 270 mcg/kg has been shown to be equally efficacious with potentially faster resolution of bleeding, convenience and decreased injection related pain.<sup>25</sup> The single high dosing regimen is used more widely in Europe, compared with USA or Canada. Recently, Fernandez-Bello et al.<sup>26</sup> evaluated TEG technology and thrombin generation assay (TGA) in the two dosing regimens, demonstrating the correlation of thromboelastography and TGA with PK studies. Additionally, the maximum thrombin generation (MTG) on the TEG highlighted the persistent hemostatic state after the 3 doses regimen for up to 9 hours. This finding may suggest the benefit of an additional 90 mcg/kg dose of rFVIIa 6–9 hours following an initial 270 mcg/kg dose to maintain hemostasis. Studies like this allow us to have objective data to assist with the use of bypassing agents.

## 5 | PERIOPERATIVE MANAGEMENT

Surgical interventions in hemophilia patients, especially those with inhibitors, require a multidisciplinary approach and meticulous planning to achieve successful outcomes.<sup>27</sup> Determining the optimal frequency and dose of factor replacement in the perioperative period is



**FIGURE 3** (A) Preferential correction of TEG 5000 parameters with aPCC compared with rFVIIa in a hemophilia a patient (FVIII < 1%) with high-titer inhibitor (26.5 BU). Tracing (A) is post 3-hour wash out from last dose of rFVIIa showing significant delay in clot initiation. Tracing (B) is post rFVIIa dose showing limited improvement in time to clot initiation. Tracing (C) is post aPCC dose showing significant improvement in time to clot initiation. (B) ROTEM analysis in a patient with severe hemophilia A and high titer inhibitor on emicizumab, showing no change from baseline after in-vitro spiking with rFVIIa (1.3 mcg/mL) and rPFVIII (1.4 U/mL), whereas the marked (\*) tracing shows spiking with aPCC (0.75 U/mL) associated with significant shortening of clot initiation time [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

key to favorable outcomes. This can be extremely difficult to do using only a FVIII assay as the test result is usually not available in real time. In patients with Factor VIII inhibitors, no factor assay can be utilized. Furukawa et al. successfully used ROTEM analysis in a 3-step protocol for preoperative planning for severe hemophilia A patients with high titer inhibitor. The first step included in vitro studies after spiking blood samples with rFVIIa and aPCC, which allowed determining the superior response and optimal dosing. Accordingly, the second step involved preoperative evaluation of the in vivo response to the agent and dosing of choice. Last, a third analysis was performed 30 minutes perioperatively to confirm adequate hemostasis.<sup>28</sup> Similarly, Croteau et al.<sup>29</sup> describe the case of a 5-year old hemophilia A patient with high-titer and refractory immune tolerance induction (ITI) undergoing high-risk cardiac surgery. TEG analysis was used in the preoperative setting to effectively assess the potential of various hemostatic agents, including recombinant porcine FVIII and aPCC. Thus, these assays can be extremely beneficial and allow the hematologist to evaluate both risks and benefits of treatment options.

Thromboelastography is particularly vital in the setting of emergent surgery in hemophilia patients; as perioperative planning is not possible, and rapidly obtained PT and aPTT are limited in the monitoring of hemostasis particularly when bypassing agents are used. Pivalizza et al. used both TEG and ROTEM technologies to monitor hemostasis during an emergent evacuation of spinal hematoma surgery. Larger doses of rFVIIa (at 200 and 300 mcg/kg) were used preoperatively and intraoperatively, guided by TEG and ROTEM parameters. An important point to delineate, is that Pivalizza et al.<sup>30</sup> employed different activators in each modality, Kaolin in TEG5000 analyzers and TF in ROTEM analyzers, yielding comparable results.

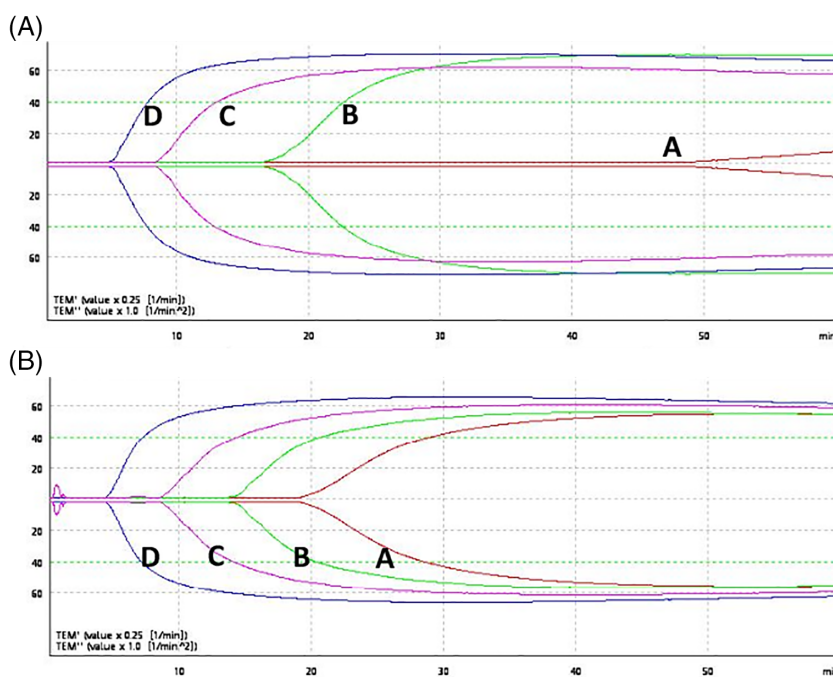
This is important to note in the ongoing quest for the optimal activator to be used with viscoelastic testing in hemophilia patients.

As higher life expectancy is achieved in patients with hemophilia, age related disorders including cardiovascular disease and requirement for cardiothoracic surgery are becoming more prevalent.<sup>31,32</sup> Cardiac surgery is a major hemostatic challenge as a result of sternotomy, the need of total heparinization, extracorporeal circulation, mild hypothermia and cardiac arrest. Bedside thromboelastography has been found to be a valuable tool during coronary artery bypass grafting surgery by Misgav et al.<sup>33</sup>, where they utilized prolonged R time on the heparinase cup TEG analysis as an indicator of the need for additional FVIII supplementation. Heparinase cup TEG analysis eliminates the heparin effect and is a better reflection of the patient's underlying hemostatic state, which is of particular importance when systemic anticoagulation is required in hemophilia patients.

## 6 | NOVEL THERAPEUTIC APPROACHES

The emergence of novel therapeutic modalities has revolutionized the treatment of hemophilia patients, specifically those with inhibitors. Promising treatment approaches include extended half-life FVIII/FIX products, monoclonal antibodies targeting TF pathway inhibitor, siRNA targeting antithrombin, and the bispecific antibody emicizumab (Hemlibra).<sup>34</sup> These new therapeutic modalities will require new testing methodologies to monitor, as routine testing methods like CTs or factor assays cannot be used to measure their response or efficacy.

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges activated factors IX and X to restore the



**FIGURE 4** (A) Acquired inhibitor to FVIII. In-vitro studies using the ROTEM analyzer show different responses to bypassing agents and rPFVIII. Tracing (A) Baseline curve, tracing (B) Post rFVIIa (1.3 mcg/mL), tracing (C) Post rPVIII (1.4 U/mL), tracing (D) Post aPCC (0.75 U/mL). (B) Acquired inhibitor after 3 months of immunosuppressive therapy with decrease of the antibody titer (improved baseline curve) shown in tracing (A). Response to hemostatic agents remains similar to Figure 4A. Tracing (B) Post rFVIIa (1.3 mcg/mL), tracing (C): Post rPVIII (1.4 U/mL), tracing (D): Post aPCC (0.75 U/mL) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

function of deficient activated factor VIII resulting in effective hemostasis. The HAVEN trials have reported ground breaking results, showing a remarkable reduction in bleeding rates with emicizumab prophylaxis in children with hemophilia A with and without inhibitor.<sup>35-37</sup> Drug levels and novel XIa-based assays were used in the clinical trial for PK studies and hemostasis monitoring. aPTT-based FVIII assays are normal at steady state despite breakthrough bleeding episodes, raising the question if this is an artificial correction of assays from the monoclonal antibody rather than true normalized hemostasis.<sup>38,39</sup>

Figure 3B shows data from a patient with high titer inhibitors on weekly emicizumab and in-vitro spiking with bypassing agents and recombinant porcine FVIII (rPFVIII). It clearly demonstrates that his baseline coagulation does not change with rFVIIa and rPFVIII but greatly enhances with the use of aPCC. This is a particularly interesting albeit an isolated finding, as the use of aPCC averaging at 100 U/kg for more than 1 day during emicizumab prophylaxis was linked to the occurrence of thrombotic microangiopathy and thrombotic events in 5 patients in the HAVEN1 trial.<sup>35</sup> We have not observed similar findings in our aforementioned patient with high-titer inhibitor in Figure 3A, who was initiated on weekly emicizumab with dramatic response. When he presented with thrombotic microangiopathy following treatment with aPCC for 5 days for ankle bleeding while on emicizumab prophylaxis, thromboelastography parameters were not suggestive of an enhanced hemostatic state. Thus, indicating that further studies are necessary to validate the sensitivity of viscoelastic studies in the monitoring of patients on innovative therapeutic agents.

## 7 | ACQUIRED HEMOPHILIA

Acquired inhibitors against FVIII are an autoimmune disorder that affects mostly older individuals and young females during pregnancy or the postpartum period.<sup>40,41</sup> Half of the cases are idiopathic and bleeding is usually spontaneous and can be life-threatening. Treatment of hemorrhages is done with bypassing agents or recombinant porcine FVIII.<sup>42</sup> Figure 4A depicts a patient with an acquired inhibitor titer of 55 Bethesda units (BU) and the in-vitro response to bypassing agents and rPFVIII. Figure 4B depicts the same patient 3 months later (inhibitor titer of 12 BU) after treatment with immunosuppressants and improvement of her baseline curve and bleeding episodes, although the in-vitro response to hemostatic agents did not change.

## 8 | LIMITATIONS AND FUTURE OPPORTUNITIES

Despite the promising applications of viscoelastic testing in hemophilia, experience thus far is based on small sized studies and case reports while larger randomized studies are lacking. Broader utilization is limited by preanalytical and analytical factors. The blood sample should be obtained via a 21-gauge or larger needle and analyzed within 4 hours of collection to minimize platelet activation. The older viscoelastic instruments are sensitive to vibration, and manual

pipetting is required with the use of TEG 5000 while ROTEM delta utilizes automatic pipetting. Furthermore, the aforementioned controversies regarding the choice of the viscoelastic activators (extrinsic vs intrinsic activation), and the source and concentration of TF was a major drawback to the use of extrinsic activators with the TEG 5000. The newer models, TEG 6 seconds and the ROTEM sigma, have integrated cartridges prefilled with reagents aiming to improve practicality of use and precision. In light of changes in methodology, studies are necessary to determine if the newer technologies have better reproducibility and sensitivity which were issues with the prior models.

Standardization and quality assurance of viscoelastic testing is challenged by the inter operator and inter laboratory variation. Coefficients of variation of 2.6%-11.2% for ROTEM delta and 7.4%-19% for TEG 5000 parameters were reported in a study with 7 operators.<sup>43</sup> Comparison of inter laboratory external quality assurance samples have shown inferior precision of 7%-49% for TEG 5000 and 7%-83% for ROTEM delta.<sup>44</sup> Similar to the standardization of PFA-100, another whole blood assay, this can be hopefully overcome by utilizing externally standardized reagents and methods for local quality assurance. Additionally, standardization can be further facilitated by the development of easier to use technologies, such as the cartridge based TEG 6 seconds analyzer. This will help reduce variance and allow for superior external quality control and inter and intra-laboratory comparability.

The introduction of new therapies may require new activators or other modifications of currently available viscoelastic testing systems. If successfully addressed this may ultimately result in the increased utilization of viscoelastic studies as current conventional coagulation testing does not fully address the clinical need.

## CONFLICT OF INTEREST

Dr. Hartmann is a Vice President and Head of Medical Affairs and Clinical Development at Haemonetics. Previously he was an Associate Partner in the global Medical Affairs practice at McKinsey & Co., Inc., where he led the hemophilia disease area team. The other authors do not have any relevant conflicts of interest to disclose.

## ORCID

Jan Hartmann  <https://orcid.org/0000-0003-4978-8014>

## REFERENCES

1. Hartert H. Blutgerinnungsstudien mit der Thrombelastographie; einem neuen Untersuchungsverfahren. *Klin Wochenschr.* 1948;26(37-38): 577-583.
2. Nogami K. The utility of thromboelastography in inherited and acquired bleeding disorders. *Br J Haematol.* 2016;174(4):503-514. <https://doi.org/10.1111/bjh.14148>.
3. Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. *Am J Hematol.* 2014;89(2):228-232. <https://doi.org/10.1002/ajh.23599>.
4. Chitlur M, Simpson ML. Role of global assays in thrombosis and thrombophilia. In: Goldenberg NA, Manco-Johnson MJ, eds. *Pediatric Thrombotic Disorders*. Cambridge: Cambridge University Press; 2014: 142-157. <https://doi.org/10.1017/CBO9781139028882.012>.
5. Young G, Sorensen B, Dargaud Y, Negrier C, Brummel-Ziedins K, Key NS. Thrombin generation and whole blood viscoelastic assays in

- the management of hemophilia: current state of art and future perspectives. *Blood*. 2013;121(11):1944-1950. <https://doi.org/10.1182/blood-2012-08-378935>.
6. Mohammed BM, Martin EJ, Salinas V, Carmona R, Young G, Brophy DF. Failure of corn trypsin inhibitor to affect the thrombin generation assay in plasma from severe hemophiliacs. *J Thromb Haemost*. 2014;12(9):1558-1561. <https://doi.org/10.1111/jth.12659>.
  7. Chitlur M, Young G. Global assays in hemophilia. *Semin Hematol*. 2016; 53(1):40-45. <https://doi.org/10.1053/j.seminhematol.2015.10.001>.
  8. Bolliger D, Seeberger MD, Tanaka KA. Principles and practice of thromboelastography in clinical coagulation management and transfusion practice. *Transfus Med Rev*. 2012;26(1):1-13. <https://doi.org/10.1016/J.TMRV.2011.07.005>.
  9. Lancé MD. A general review of major global coagulation assays: thromboelastography, thrombin generation test and clot waveform analysis. *Thromb J*. 2015;13:1. <https://doi.org/10.1186/1477-9560-13-1>.
  10. Hartmann J, Mason D, Achneck H. Thromboelastography (TEG) point-of-care diagnostic for hemostasis management. *Point Care J Near-Patient Test Technol*. 2018;17(1):15-22. <https://doi.org/10.1097/POC.000000000000156>.
  11. Bolton-Maggs PH, Pasi KJ. Haemophilias a and B. *Lancet*. 2003; 361(9371):1801-1809. [https://doi.org/10.1016/S0140-6736\(03\)13405-8](https://doi.org/10.1016/S0140-6736(03)13405-8).
  12. Sorensen B, Ingerslev J. Whole blood clot formation phenotypes in hemophilia a and rare coagulation disorders. Patterns of response to recombinant factor VIIa. *J Thromb Haemost*. 2004;2(1):102-110. <https://doi.org/10.1111/j.1538-7836.2004.00528.x>.
  13. Chitlur M, Warriar I, Rajpurkar M, et al. Thromboelastography in children with coagulation factor deficiencies. *Br J Haematol*. 2008;142(2): 250-256. <https://doi.org/10.1111/j.1365-2141.2008.07063.x>.
  14. Salinas V, Carmona R, Mohammed BM, Martin EJ, Brophy DF, Young G. Is some better than none: are TEG and TGA profiles different in severe FVIII-deficient patients with inhibitors? *Haemophilia*. 2015;21(3):398-404. <https://doi.org/10.1111/hae.12578>.
  15. Tarandovskiy ID, Balandina AN, Kopylov KG, et al. Investigation of the phenotype heterogeneity in severe hemophilia a using thromboelastography, thrombin generation, and thrombodynamics. *Thromb Res*. 2013;131(6):e274-e280. <https://doi.org/10.1016/j.thromres.2013.04.004>.
  16. Bowyer AE, Van Veen JJ, Goodeve AC, Kitchen S, Makris M. Specific and global coagulation assays in the diagnosis of discrepant mild hemophilia a. *Haematologica*. 2013;98(12):1980-1987. <https://doi.org/10.3324/haematol.2013.088088>.
  17. van Veen JJ, Gatt A, Bowyer AE, Cooper PC, Kitchen S, Makris M. Calibrated automated thrombin generation and modified thromboelastometry in haemophilia a. *Thromb Res*. 2009;123(6):895-901. <https://doi.org/10.1016/j.thromres.2008.09.011>.
  18. AL Hawaj MA, Martin EJ, Venitz J, et al. Monitoring rFVIII prophylaxis dosing using global haemostasis assays. *Haemophilia*. 2013;19(3):409-414. <https://doi.org/10.1111/hae.12110>.
  19. Negrier C, Goudemand J, Sultan Y, Bertrand M, Rothschild C, Lauroua P. Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. French FEIBA study group. Factor eight bypassing activity. *Thromb Haemost*. 1997;77(6):1113-1119.
  20. Parameswaran R, Shapiro AD, Gill JC, Kessler CM. HTRS Registry investigators. Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the hemophilia and thrombosis research society Registry. *Haemophilia*. 2005;11(2):100-106. <https://doi.org/10.1111/j.1365-2516.2005.01075.x>.
  21. Astermark J, Donfield SM, DiMichele DM, et al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven comparative (FENOC) study. *Blood*. 2007; 109(2):546-551. <https://doi.org/10.1182/blood-2006-04-017988>.
  22. Hayashi T, Tanaka I, Shima M, et al. Unresponsiveness to factor VIII inhibitor bypassing agents during hemostatic treatment for life-threatening massive bleeding in a patient with hemophilia a and a high responding inhibitor. *Haemophilia*. 2004;10(4):397-400. <https://doi.org/10.1111/j.1365-2516.2004.00924.x>.
  23. Dunkley SM, Yang K. The use of combination FEIBA and rFVIIa bypassing therapy, with TEG profiling, in uncontrollable bleeding associated with acquired haemophilia A. *Haemophilia*. 2009;15(3):828-830.
  24. Young G, Blain R, Nakagawa P, Nugent DJ. Individualization of bypassing agent treatment for haemophilic patients with inhibitors utilizing thromboelastography. *Haemophilia*. 2006;12(6):598-604. <https://doi.org/10.1111/j.1365-2516.2006.01319.x>.
  25. Pan-Petesches B, Laguna P, Mital A, et al. Single-dose (270 microg kg [-1]) recombinant activated factor VII for the treatment and prevention of bleeds in haemophilia a patients with inhibitors: experience from seven European haemophilia centres. *Haemophilia*. 2009;15(3): 760-765. <https://doi.org/10.1111/j.1365-2516.2008.01968.x>.
  26. Fernández-Bello I, Stenmo C, Butta N, Lind V, Ezban M, Jiménez-Yuste V. The pharmacokinetics and pharmacodynamics of single-dose and multiple-dose recombinant activated factor VII in patients with haemophilia A or B. *Haemophilia*. 2017;23:868-876. <https://doi.org/10.1111/hae.13312>.
  27. Escobar M, Brewer A, Caviglia H, et al. Recommendations on multidisciplinary management of elective surgery in people with haemophilia. *Haemophilia*. 2018;24:1-10. <https://doi.org/10.1111/hae.13549>.
  28. Furukawa S, Nogami K, Ogiwara K, Yada K, Minami H, Shima M. Systematic monitoring of hemostatic management in hemophilia a patients with inhibitor in the perioperative period using rotational thromboelastometry. *J Thromb Haemost*. 2015;13(7):1279-1284. <https://doi.org/10.1111/jth.12987>.
  29. Croteau SE, Abajas YL, Wolberg AS, et al. Recombinant porcine factor VIII for high-risk surgery in paediatric congenital haemophilia A with high-titre inhibitor. *Haemophilia*. 2017;23(2):e93-e98. <https://doi.org/10.1111/hae.13157>.
  30. Pivalizza EG, Escobar MA. Thromboelastography-guided factor VIIa therapy in a surgical patient with severe hemophilia and factor VIII inhibitor. *Anesth Analg*. 2008;107(2):398-401. <https://doi.org/10.1213/ane.0b013e31817b7864>.
  31. Fogarty PF, Mancuso ME, Kasthuri R, et al. Presentation and management of acute coronary syndromes among adult persons with haemophilia: results of an international, retrospective, 10-year survey. *Haemophilia*. 2015;21(5):589-597. <https://doi.org/10.1111/hae.12652>.
  32. Tang M, Wierup P, Terp K, Ingerslev J, Sørensen B. Cardiac surgery in patients with haemophilia. *Haemophilia*. 2009;15(1):101-107.
  33. Misgav M, Mandelbaum T, Kassif Y, Berkenstadt H, Tamarin I, Kenet G. Thromboelastography during coronary artery bypass grafting surgery of severe hemophilia a patient—the effect of heparin and protamine on factor VIII activity. *Blood Coagul Fibrinolysis*. 2017;28(4): 329-333. <https://doi.org/10.1097/MBC.0000000000000575>.
  34. Hartmann J, Croteau SE. 2017 clinical trials update: innovations in hemophilia therapy. *Am J Hematol*. 2016;91(12):1252-1260. <https://doi.org/10.1002/ajh.24543>.
  35. Oldenburg J, Mahlangu JN, Kim B, et al. Efficacy of emicizumab prophylaxis in hemophilia a with inhibitors. *N Engl J Med*. 2017;377(9):809-818. <https://doi.org/10.1056/NEJMoa1703068>.
  36. Young G, Sidonio RF, Liesner R, et al. HAVEN 2 updated analysis: multicenter, open-label, phase 3 study to evaluate efficacy, safety and pharmacokinetics of subcutaneous Administration of Efficacy of Emicizumab Prophylaxis in pediatric patients with hemophilia a with inhibitors. *Blood*. 2017;130(Suppl 1):85.
  37. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Efficacy of emicizumab prophylaxis in patients who have hemophilia a without inhibitors. *N Engl J Med*. 2018;379(9):811-822. <https://doi.org/10.1056/NEJMoa1803550>.
  38. Al-Samkari H, Croteau SE. Shifting landscape of hemophilia therapy: implications for current clinical laboratory coagulation assays. *Am J Hematol*. 2018;93:1082-1090. <https://doi.org/10.1002/ajh.25153>.
  39. Shima M, Hanabusa H, Taki M, et al. Long-term safety and efficacy of emicizumab in a phase 1/2 study in patients with hemophilia A with or without inhibitors. *Blood Adv*. 2017;1:1891-1899.
  40. Knoebel P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia a: results from the European acquired Haemophilia Registry (EACH2). *J Thromb Haemost*. 2012;10(4):622-631. <https://doi.org/10.1111/j.1538-7836.2012.04654.x>.
  41. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia a in the United Kingdom: a 2-year national surveillance study by the United

- Kingdom Haemophilia Centre Doctors' organisation. *Blood*. 2007; 109(5):1870-1877. <https://doi.org/10.1182/blood-2006-06-029850>.
42. Baudo F, Collins P, Huth-Kühne A, et al. Management of bleeding in acquired hemophilia a: results from the European acquired Haemophilia (EACH2) Registry. *Blood*. 2012;120(1):39-46. <https://doi.org/10.1182/blood-2012-02-408930>.
43. Anderson L, Quasim I, Steven M, et al. Interoperator and Intraoperator variability of whole blood coagulation assays: a comparison of Thromboelastography and rotational thromboelastometry. *J Cardiothorac Vasc Anesth*. 2014;28(6):1550-1557. <https://doi.org/10.1053/j.jvca.2014.05.023>.
44. Kitchen D, Kitchen S, Jennings I, Woods T, Walker I. Quality assurance and quality control of thrombelastography and rotational

thromboelastometry: the UKNEQAS for blood coagulation experience. *Semin Thromb Hemost*. 2010;36(07):757-763. <https://doi.org/10.1055/s-0030-1265292>.

**How to cite this article:** Ramiz S, Hartmann J, Young G, Escobar MA, Chitlur M. Clinical utility of viscoelastic testing (TEG and ROTEM analyzers) in the management of old and new therapies for hemophilia. *Am J Hematol*. 2019;94: 249–256. <https://doi.org/10.1002/ajh.25319>