Received: 14 March 2023 | Accepted: 25 July 2023

DOI: 10.1111/ijlh.14144

REVIEW

ISLH International Journal of Laboratory Hematology WILEY

Viscoelastic testing: Critical appraisal of new methodologies and current literature

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Abstract

United States Food and Drug Administration (FDA)-approved viscoelastic testing (VET) methodologies have significantly changed in the last 10 years, with the availability of cartridge-based VET. Some of these cartridge-based methodologies use harmonic resonance-based clot detection. While VET has always allowed for the evaluation of real-time clot formation, cartridge-based VET provides increased ease of use as well as greater portability and robustness of results in out-of-laboratory environments. Here we review the use of VET in a variety of clinical contexts, including cardiac surgery, trauma, liver transplant, obstetrics, and hypercoagulable states such as COVID-19. As of now, high quality randomized trial evidence for new generation VET (TEG 6s, HemoSonics Quantra, ROTEM sigma) is limited. Nevertheless, the use of VET-guided transfusion algorithms appears to result in reduced blood usage without worsening of patient outcomes. Future work comparing the new generation VET instruments and continuing to validate clinically important cut-offs will help move the field of point-of-care coagulation monitoring forward and increase the quality of transfusion management in bleeding patients.

KEYWORDS
blood transfusion, fibrinogen, fibrinolysis, hemostasis, laboratory practice, platelets

1 | INTRODUCTION

Viscoelastic testing (VET) refers to a group of coagulation testing methods which assess the physical properties of clot formation in a whole blood sample in real-time. Unlike traditional coagulation testing methods, VET simultaneously assesses multiple physiologic contributors to clot formation such as platelet number and function, fibrin polymerization, and other plasmatic coagulation factors. Red cells and white cells in the whole blood sample may also play a role. VET monitors clot formation with a live wavetrace, with various curve parameters reflecting corresponding physiologic contributors.[1]

Conventional coagulation laboratory testing (CCT) is very inexpensive on a per-test basis, with typical laboratory reagent costs for PT, aPTT, and fibrinogen testing being on the order of 1–5 USD per assay. CCT generally yields singular points of quantitative data and accurately assesses specific contributors to hemostasis, but individually provide an incomplete review of the hemostatic milieu. Most significantly, CCTs do not consider the functional contribution of the cellular component of clotting, including those of platelets. VET methods yield rapidly actionable laboratory data that can influence clinical management of coagulopathies and anticoagulation. VET methods do not require sample centrifugation, and new generation methods require no test preparation beyond transfer pipetting or sample tube spiking. These method

improvements allow greater portability and ease of use at or near the point of care. The formation of a VET trace occurs in real time and can yield information within minutes of test initiation, and the review of trace formation can be performed via remote computer interface to inform clinical practice even when testing is performed in the laboratory setting. Despite the additional per-test costs as compared to CCT, use of VET-based transfusion algorithms have been found to reduce the average overall cost of care for patients requiring transfusion, likely due to a decrease in length of hospital stay.[2] A 2015 National Institute for Health and Care Research (NIHR) review of VET methods concluded them to be more cost-effective than CCT in management of cardiac and especially trauma patients.[3] A 2014 National Institute for Health and Care Excellence (NICE) review supported VET use in cardiac surgery and identified decreases in red cell, plasma, and platelet usage when VET methods are used.[4] It should be noted that VET results correlate with CCT assays, but are not interchangeable.[5] A comparison of strengths and weaknesses of VET and CCT assays is provided in Table 1.

VET-guided transfusion algorithms are of greatest benefit in operative settings where high blood loss is expected and where coagulopathies are common—particularly cardiac surgery, trauma, and liver transplant. Use of VET-guided transfusion strategies reduces the need for blood products and improves morbidity in bleeding patients.[6–13] However, VET does not completely recapitulate in vivo clotting. Whereas physiologic clotting occurs under conditions of flowing blood and in the presence of the vascular endothelium and collagen, VET methods rely on evaluation of a static blood sample in a plastic vessel. For this reason, current VET reagents are insensitive to von Willebrand disease.[14] While there is little data available, VET is also generally insensitive to deficiencies of protein C and S and antithrombin.[14]

Here we will focus on recent developments in United States Food and Drug Administration (FDA)-approved VET, including TEG 6s, ROTEM sigma, and HemoSonics Quantra.

TABLE 1 Conventional coagulation testing (CCT) versus viscoelastic testing (VET): Pros and Cons.

Conventional coagulation testing (CCT)	Viscoelastic testing (VET)
Test performance	
Requires central laboratory and transport	Can be performed centrally or at point of care
Requires centrifuged citrated plasma	Requires citrated whole blood
Slow turnaround (1 h)	Rapid turnaround (30–60 min for complete trace, <10 min for actionable data)
Numerical result reporting only	Live wavetrace viewability
High precision and reproducibility	Less precise than plasma-based CCT
Poor at predicting bleeding events	Poor at predicting bleeding events
Cost-effectiveness	
Inexpensive	High per-test cost
	Associated with decreased transfusion volumes and in-hospital costs compared to CCT
Unique applications and benefits	
Gold standard assays with decades of clinical experience	Can detect hyperfibrinolysis
Availability of D-dimer measurement	Can detect hypercoagulability
	No need for centrifugation

2 | DETECTION OF CLOTTING BY VET

A clot is composed of a scaffolding of platelets and polymerized fibrin(ogen) connected through the interaction of platelet glycoprotein IIb/IIIa receptors. Red blood cells (RBCs) and white blood cells also contribute to bulk of this structure. The formation of this cell and fibrin(ogen) meshwork underlies the physical transition of blood from a liquid state to a solid-gel state. The solid-gel state is able to resist deformation under physical shear forces, a property called elasticity which is measured by the shear modulus. As clotting blood transitions into the solid-gel state, the shear modulus increases due to the formation of the comparably rigid platelet-fibrin(ogen) meshwork. Use of platelet inhibitors such as abciximab or cytochalasin D allows specific assessment of fibrinogen contribution to clot strength.[1]

The shear modulus can be assessed either by mechanical probing of the forming clot, as in traditional TEG and ROTEM assays (often referred to as *legacy* VET methods), or by sonometric methods. In legacy methods, formation of the clot is physically transduced by a central pin around which a clot is formed. As the clot forms and adheres to the pin as well as the walls of the reaction vessel, an externally applied force becomes transmitted through the clot, and the change in pin movement is used to generate the viscoelastic wavetrace. These legacy methods are variably sensitive to ambient conditions such as vibrations in the testing environment.

In contrast, sonometric methods determine the shear modulus by exploiting the physical tendency of solids to resonate in response to vibrational stimuli. Upon application of a vibrational stimulus, liquids and solids differ in their oscillation responses. The frequency at which the least vibrational dampening occurs is the resonance frequency, and this frequency is influenced by the physical makeup of the solid and is thus related to the shear modulus. The resonance frequency can be detected by interrogation with sonometric pulses and an accompanying detection method (discussed below). The viscoelastic wavetrace can be computationally generated by continuous detection of the resonance signal. These sonometric methods are more resistant to ambient testing conditions.

3 | CURRENT METHODS

3.1 | Legacy platforms

The two oldest licensed viscoelastic testing techniques are TEG 5000 (Haemonetics, Boston, MA) and ROTEM delta (Werfen,

TABLE 2 Viscoelastic tests.

Platform/cartridge	Test	Reagent, in addition to $CaCl_2$ (concentration listed if available)	Utility
TEG 5000	CK	Kaolin	Sensitive to intrinsic pathway
	CKH	Kaolin Heparinase (2.0 IU)	Compare R-time with that of K-TEG to identify heparin effect
	Citrated Rapid TEG (rTEG or CRT)	Kaolin Tissue factor	Clot immediately forms, allowing rapid interpretation of amplitude.
	CFF	Kaolin Tissue factor Abciximab	Maximal amplitude reflects contribution of fibrinogen to clot strength absent any platelet function.
ROTEM delta	INTEM	Ellagic acid	Sensitive to intrinsic pathway
	HEPTEM	Ellagic acid Heparinase	Compare CT with that of INTEM to identify heparin effect
	EXTEM	Tissue factor Polybrene	Clot immediately forms, allowing rapid interpretation of amplitude.
	FIBTEM	Tissue factor Polybrene Cytochalasin D	Maximal clot formation reflects contribution of fibrinogen to clot strength absent any platelet function.
	APTEM	Tissue factor Polybrene Aprotinin	Compare LI30/LI60 with that of EXTEM to confirm hyperfibrinolysis.
Platelet mapping (can be performed on TEG 5000 or TEG 6s)	"A"	Reptilase Factor XIIIa	Determine fibrinogen's contribution to clot maximal amplitude
	Thrombin	Reptilase Factor XIIIa Kaolin	Determine maximal platelet contribution to clot maximal amplitude
	AA	Reptilase + Factor XIIIa Arachidonic acid (1 mM AA with TEG 5000)	Assess for aspirin effect relative to thrombin and "A" channels
	ADP	Reptilase + Factor XIIIa ADP (2 μM ADP with TEG 5000)	Assess for P2Y12 inhibitor effect relative to thrombin and "A" channels
TEG 6 s Global Hemostasis	CK	Kaolin	Assess coagulation factors, inhibitors Cannot report clot lysis
	CKH	Kaolin Heparinase	Confirm presence of heparin
	CRT	Kaolin Tissue factor	Rapidly assess platelets and fibrinogen
	CFF	Kaolin Tissue factor Abciximab	Rapidly assess fibrinogen
TEG 6 s "Trauma" (Global Hemostasis with Lysis)	CK	Kaolin	Assess coagulation factors, inhibitors Can report clot lysis
	CRT	Kaolin Tissue factor (2 μg/mL)	Rapidly assess platelets and fibrinogen
	CFF	Kaolin Tissue factor (0.3 μg/mL) Abciximab (2 mg/mL)	Rapidly assess fibrinogen
ROTEM sigma Complete	INTEM	Ellagic acid	Assess coagulation factors, inhibitors
	EXTEM	Tissue factor Polybrene	Rapidly assess platelets and fibrinogen
	FIBTEM	Tissue factor Polybrene Cytochalasin D	Rapidly assess fibrinogen

(Continues)

TABLE 2 (Continued)

Platform/cartridge	Test	Reagent, in addition to $CaCl_2$ (concentration listed if available)	Utility
	APTEM	Tissue factor Polybrene Aprotinin	Confirm presence of hyperfibrinolysis
ROTEM sigma Complete + Hep	INTEM	Ellagic acid	Assess coagulation factors, inhibitors
	EXTEM	Tissue factor Polybrene	Rapidly assess platelets and fibrinogen
	FIBTEM	Tissue factor Polybrene Cytochalasin D	Rapidly assess fibrinogen
	HEPTEM	Ellagic acid Heparinase	Confirm presence of heparin
Quantra QPlus	Channel 1	Kaolin	Assess coagulation factors, inhibitors
	Channel 2	Kaolin Heparinase	Confirm presence of heparin
	Channel 3	Tissue factor Polybrene	Rapidly assess platelets and fibrinogen
	Channel 4	Tissue factor Polybrene Abciximab	Rapidly assess fibrinogen
Quantra Qstat	Channel 1	Kaolin	Assess coagulation factors, inhibitors
	Channel 2	Kaolin Tranexamic acid	Confirm presence of hyperfibrinolysis
	Channel 3	Tissue factor Polybrene	Rapidly assess platelets and fibrinogen
	Channel 4	Tissue factor Polybrene Abciximab	Rapidly assess fibrinogen

Note: On each legacy platform, reagents are loaded by manual pipetting with one test per cup and either two (TEG 5000) or four (ROTEM delta) cups per instrument. On each new generation platform (TEG 6s, ROTEM sigma, HemoSonics Quantra), cartridges are pre-formulated with lyophilized reagent across three or four channels/reaction chambers, allowing for simultaneous and rapid assessment of coagulation factors, platelets, fibrinogen, fibrinolysis, and heparin effect.

Barcelona, Spain). They report fundamentally similar metrics but with different parameter nomenclature. They also differ in the reagents utilized (Table 2), in particular their clotting activators. Results from TEG and ROTEM testing are not interchangeable,[15] even with similar activators, and consecutive VET analysis should be limited to one platform, ideally with a comparison to a patient's "baseline" to guide interpretation when possible. Baseline viscoelastic testing is infrequently collected and sparsely represented in the literature, however.[16]

Both instruments involve adding whole blood, calcium chloride, and clotting activators to a cup, which is heated to 37°C and into which a pin is immersed.

3.1.1 | TEG 5000

(Figure 1A) This platform utilizes a stationary pin and a rotating cup. The cup slowly undergoes periodic and alternating rotations (4.75° arc every 5 s). As a clot forms, it transmits torque from the cup walls to the pin. The rotation of the pin is detected by a torsion wire and this signal is converted directly into the viscoelastic wavetrace. TEG 5000 reagents and curve parameters are shown in Figure 2. TEG 5000 can run two cups simultaneously.

As of this writing, the Haemonetics Corporation has announced plans to stop manufacturing the TEG 5000 instrument and will terminate device support in 2029.

3.1.2 | ROTEM delta

(Figure 1B) This platform utilizes a rotating pin and a stationary cup. The pin rotates slowly on a spring-driven axis (4.75° arc every 6 s). The axis also bears a mirror upon which a light beam is focused. As the clot forms, it impedes the rotation of the pin, decreasing the amplitude of oscillation. This decrease is captured by a photodetector and converted into the viscoelastic wavetrace.

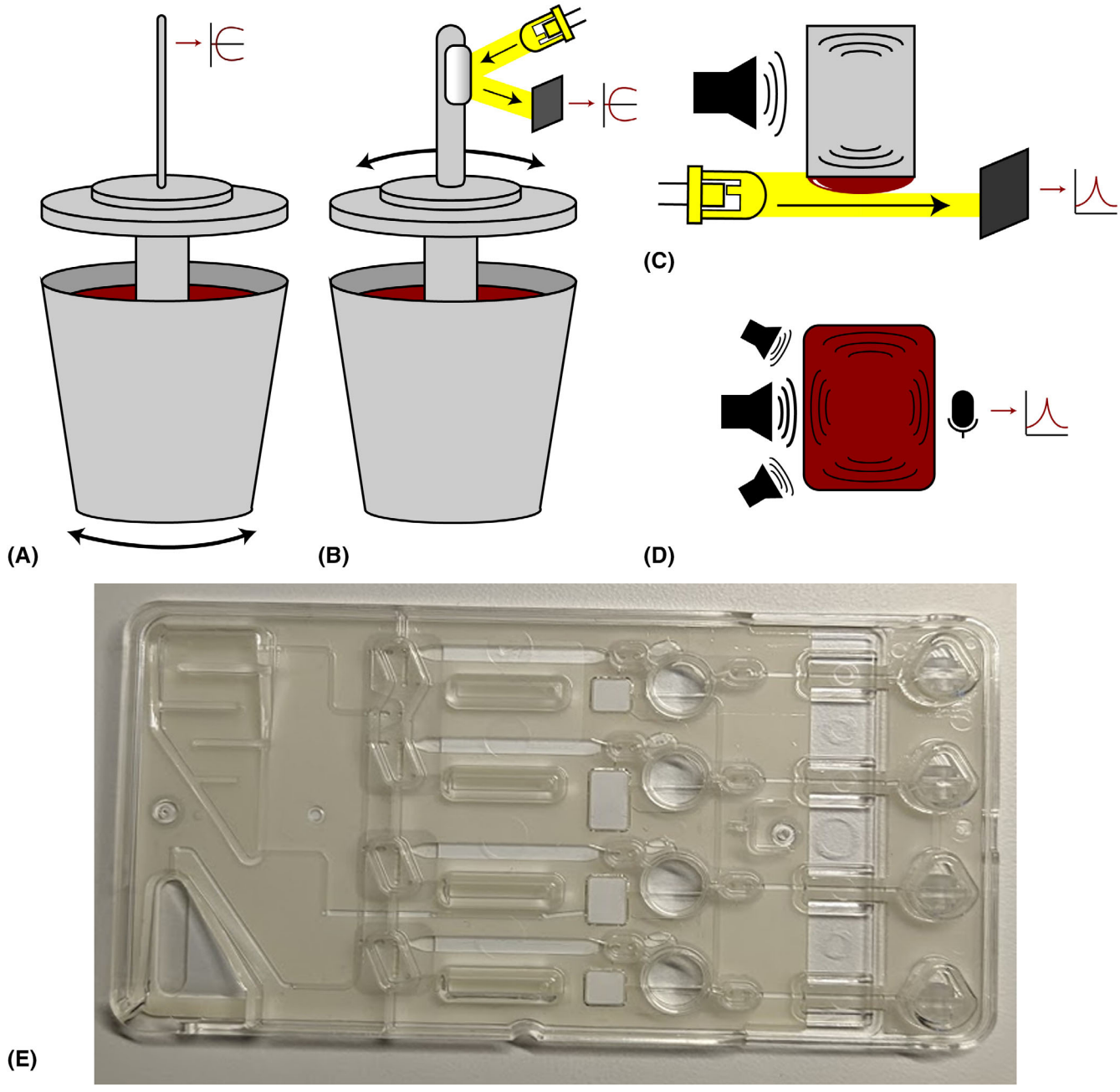
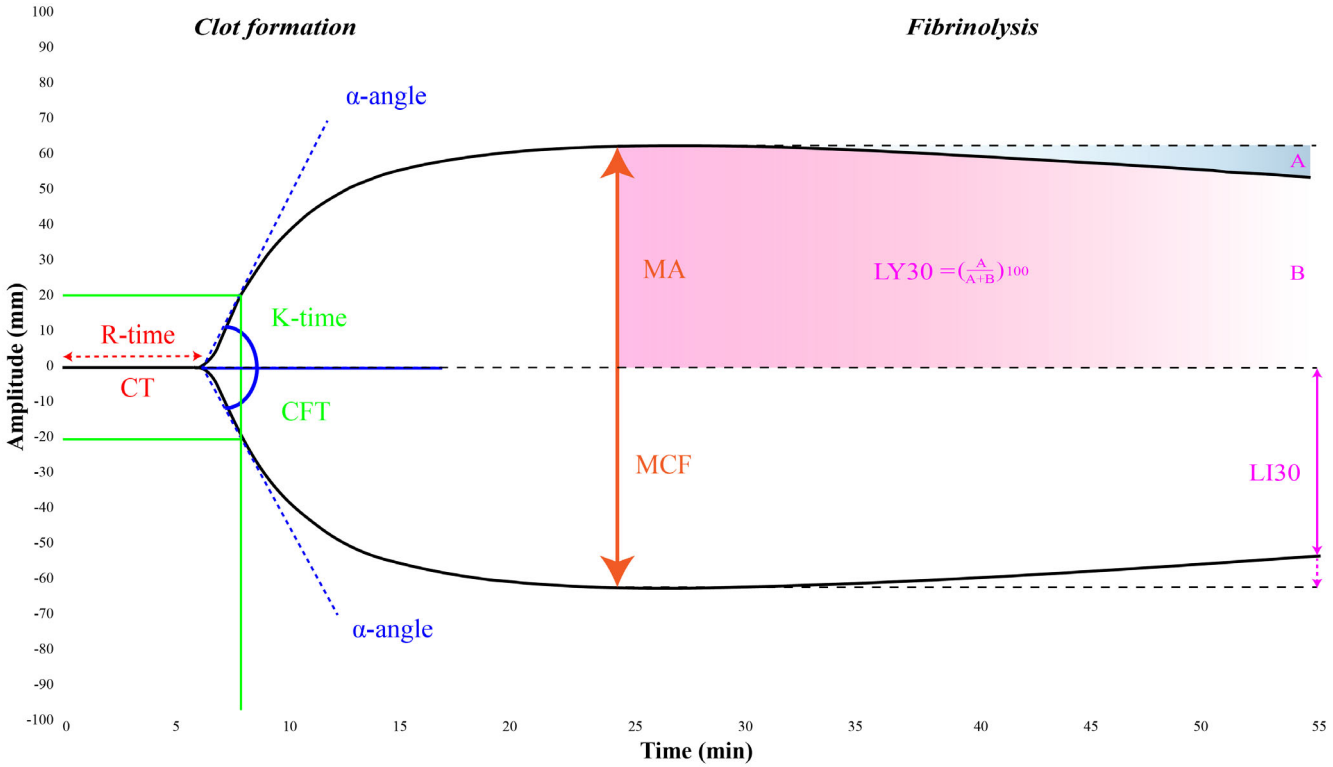


FIGURE 1 Common viscoelastic testing methods. From Carll et al.[1] (A) TEG 5000 utilizes a rotating cup and stationary pin connected to a torsion wire which mechanically transduces force upon clot formation, generating the wavetrace. (B) ROTEM delta utilizes a stationary cup and rotating pin which is impeded upon clot formation; changes in light reflectance by a mirror on the rotating axis is used to generate the wavetrace. (C) TEG 6s applies vibrational stimuli and measures resonance of a meniscus by changes in light transmittance. (D) HemoSonics Quantra relies on an ensemble of sonometric pulses, both to induce shear waves in the blood sample and to detect the magnitude of deformations induced by the shear waves. (E) TEG 6s cartridges contain four microfluidics channels with lyophilized reagents. Detection of clot formation is performed by detection of light transmittance past a meniscus that forms at the end of each channel (right).

ROTEM reagents and curve parameters are shown in Figure 2. Unlike TEG, ROTEM has a tissue factor-only reagent (EXTEM) and an aprotinin reagent which confirms that apparent fibrinolysis is due to plasmin and not artifactual clot dislodgment from the pin (APTEM). ROTEM delta can run four cups simultaneously.

3.2 | Cartridge-based platforms (TEG 6s, ROTEM sigma, HemoSonics Quantra)

Disposable microfluidics VET cartridges contain lyophilized clot activators, making manual pipetting of reagents unnecessary.



	TEG	ROTEM	Quantra	Contributors
Time to initial clot formation	R-time	CT	CT	Plasmatic coagulation factors other than fibrinogen
Rate of initial clot formation	K-time α-angle	CFT α-angle	-	Fibrinogen >> platelets
Mature clot strength	MA	MCF	CS PCS, FCS	Varies depending on reagent
Clot lysis	LY30 LY60	LI30 LI60	CSL	tPA, PAI-1, plasmin, fibrinogen, factor XIII

FIGURE 2 Viscoelastic wavetrace and parameters. From Carll et al.[1] A trace typical of a normal healthy donor is depicted. Instrument signal is displayed on the *Y*-axis against time on the *X*-axis. Parameters reported by TEG testing methods are displayed on the top half of the wavetrace, while the corresponding parameters reported by ROTEM testing methods are displayed on the bottom half. These parameters are very similar with the notable exception of the LY30/LY60 and LI30/LI60, of which the former is calculated using area-under-curve analysis while the latter is expressed as a simple percentage reduction from the MCF.

The TEG 6s instrument requires transfer pipetting of whole blood into the cartridge while the ROTEM sigma and HemoSonics Quantra allows spiking of the specimen tube directly onto the cartridge. These updates improve ease of use and may reduce user error. These instruments show improved testing consistency and are more portable than their predecessors. Cartridge-based VET platforms remain classified as moderate complexity testing under CLIA '88. Cartridge-based platforms are approved for use with citrated whole blood samples only.

3.2.1 | TEG 6s

(Figure 1C,E) Once added to the cartridge, blood is divided into multiple channels, each containing different reagents. Clot formation in each channel is assessed simultaneously by the formation of a meniscus in a chamber at the end of the channel, which partially blocks light transmittance from a photodiode in the instrument. The reaction chamber is subjected to sound frequencies ranging from 20 to 500 Hz, and the motion of the meniscus is observed by an optical

detector. The resonance frequency of the clotting pendant blood drop is identified as the frequency associated with the greatest degree of meniscal displacement. The light transmittance data is converted and reported as legacy parameters identical to that of the TEG 5000, with computed generation of the familiar wavetrace.

Currently, three different TEG 6s cartridges are FDA-approved and available for use in the United States.

1. The global hemostasis cartridge includes four channels: Kaolin (CK), kaolin and heparinase (CKH), tissue factor and kaolin (Rapid TEG, CRT, or "rTEG"), and tissue factor and abciximab (CFF). This cartridge is approved for use in adults undergoing cardiac procedures. Of note, limitations of FDA approval and software programming can make real-life heparin monitoring suboptimal (CK R times >17 min are not quantified and non-R time parameters are not reported with the CKH reagent), particularly with high dose heparin used in cardiopulmonary bypass (CPB). This cartridge does not monitor fibrinolysis.
2. The global hemostasis with lysis ("trauma") cartridge includes three channels: Kaolin (CK), tissue factor and kaolin (rTEG), and tissue factor and abciximab (CFF). Unlike the global hemostasis cartridge, the trauma cartridge can assess fibrinolysis (LY30 is assessed on the CK channel).
3. The platelet mapping (TEG-PM) cartridge allows for assessment of platelet function in the setting of antiplatelet therapy with aspirin or P2Y12 receptor blockers. This cartridge is described in greater depth below (see Platelet function testing section). It is indicated for use primarily in cardiology settings.

The performance of the TEG 6s in clinical practice has been found to be equivalent or superior to that of the TEG 5000, with slightly improved intra-device repeatability. The TEG 5000 and 6s instrument results are not interchangeable.[17,18]

3.2.2 | ROTEM sigma

Like its predecessor, the new ROTEM sigma platform relies on mechanical transduction of clot formation via cup and rotating pin. Once a citrated vacutainer is spiked onto the ROTEM sigma cartridge, the citrated whole blood is distributed into four chambers which are interrogated simultaneously by rotating pins. Results are reported using the same parameters as on the ROTEM delta. The ROTEM sigma received FDA approval for use in clinical settings in 2022, and two cartridges are currently available:

1. Complete, which contains channels for the INTEM, EXTEM, FIBTEM, and APTEM (Table 1), intended for use in trauma settings. At the time of writing, this cartridge is not available in the US.
2. Complete + hep, which replaces the APTEM channel with a HEPTEM channel, intended for use in cardiac surgery and other heparinized settings. This cartridge received FDA approval in July 2022.

Comparative studies have shown results of ROTEM sigma assays to correlate strongly with those of the ROTEM delta[19] and TEG 6s,[20] but the instruments still cannot be used interchangeably.

3.2.3 | Quantra

(Figure 1D) The Quantra system (HemoSonics, Charlottesville, VA) uses sonorrheometry to monitor clot formation within cartridge-based microfluidics channels, similar to the TEG 6s. Each microfluidics channel again contains lyophilized reagent, and in contrast to TEG 6s, clot formation is assessed entirely by sonometric, not optical interrogation. The collected data are used to generate a time-displacement curve to describe motion of the forming clot, which can then be analyzed to identify the evolving resonance frequency and to estimate the shear force modulus. The Quantra reports clot strength in proper hectopascal units rather than the historic and counter-intuitive length units (mm) used by the TEG or ROTEM platforms. This allows for the direct subtraction of fibrinogen contribution from overall clot strength to accurately calculate platelet contribution.[21,22] Finally, Quantra can display data using traditional VET waveform trace, or through a series of dials showing parameter results. This dial-based format is designed to be intuitive for personnel who otherwise lack comfort with VET interpretation.

Two Quantra cartridges are currently available:

1. The QPlus cartridge contains four channels: Kaolin, kaolin and heparinase, thromboplastin and polybrene, and thromboplastin, polybrene, and abciximab. The kaolin and kaolin + heparinase channels are used to report clot time (CT) only, while the thromboplastin and thromboplastin+abciximab channels are used to report clot strength (CS) only. The QPlus cartridge is approved for use in cardiac and major orthopedic surgery, and studies have demonstrated it to correlate strongly with legacy ROTEM[23–25] and adequately with TEG methods.[26,27] Compared to TEG CK R time, the QPlus cartridge has shorter time to CT results.[26,27] The parameters of Fibrinogen contribution to clot stiffness (FCS) and Platelet contribution to clot stiffness (PCS) with the QPlus cartridge had high negative predictive value for ruling out hypofibrinogenemia and thrombocytopenia, respectively.[28]
2. The QStat cartridge has been developed for use in trauma and liver transplant surgery. The four channels contain: Kaolin, kaolin plus tranexamic acid (TXA), thromboplastin and polybrene, and thromboplastin, polybrene, and abciximab. Clot stability to lysis (CSL) is calculated by comparing the kaolin channels with and without TXA. The QStat cartridge received FDA approval in November 2022. One study has reported reasonable agreement between the QStat assessment of fibrinolysis and lysis with the ROTEM delta.[29]

3.3 | Platelet function testing

Typical VET reagents are sensitive to thrombocytopenia but are relatively insensitive to qualitative platelet defects.[30] This is due to the

overwhelming amount of thrombin generated in whole blood in response to routine VET reagents.[30] Specialized reagents are necessary for VET-based platelet function measurement.

TEG platelet mapping (TEG-PM) is a modification of TEG testing that is available on both the TEG 5000 and TEG 6s. The principle of this assay is to compare clot strength using platelet activators ADP or arachidonic acid versus two controls:

1. Strength of fibrin-based clot alone using reptilase and FXIII (MA_{fibrin}, negative control)
2. Strength of clot with significant thrombin generation and therefore full fibrin conversion and platelet activation (MA_{kaolin}, positive control)

Expressed mathematically:

$$\%\text{Platelet inhibition} = 1 - \frac{\text{MA (ADP or AA)} - \text{MA (fibrin)}}{\text{MA (Kaolin)} - \text{MA (fibrin)}}.$$

TEG-PM does not hold an FDA indication to diagnose platelet dysfunction. Platelet Mapping is approved only to inform the dose of antiplatelet agents in patients with a known baseline MA. Normal individuals can show a significant degree of platelet inhibition and therefore attention to normal ranges and individual baselines before initiation of antiplatelet agents is important. While TEG-PM can identify patients at increased risk of bleeding during surgery due to residual antiplatelet effect,[31] Karon et al found TEG-PM to be inferior to VerifyNow or MultiPlate instruments for monitoring antiplatelet effect.[32]

Platelet function testing by ROTEM has not been FDA approved. Quantra does not have dedicated platelet function testing, though PCS has been shown to correlate with ADP response by MultiPlate, after adjusting for platelet count.[33]

4 | CLINICAL APPLICATIONS

The primary use for VET is guiding the correction of coagulopathies by blood product transfusion. Use of VET-guided replacement algorithms has been shown to reduce blood product transfusion volume and to reduce transfusion-associated morbidity.[13] Use of these transfusion algorithms has been endorsed by multiple international guidelines, as described in the Introduction, to improve cost-effectiveness and reduce unnecessary transfusions.

The literature base demonstrating the benefit of VET is heavily skewed towards adult cardiac surgery.[8] In 2018, a meta-analysis of RCT *outside* of cardiac surgery found no significant benefit to VET use.[34] Additionally, pediatric patients are markedly under-represented in the VET literature and management of such patients is often extrapolated from the adult literature. However, viscoelastic parameter normal ranges significantly differ by age, with youngest patients showing shorter CT and increased clot kinetics and strength.[35] Therefore, when VET-based transfusion algorithms are to be used in pediatrics, they should take into account the patient's age and hemostatic developmental stage.[36]

VET-based transfusion guidances vary, but selected examples for TEG and ROTEM testing are provided in Table 3. TEG and ROTEM clot strength parameters (with non-platelet inhibited reagents) have been reported to have good correlation with platelet count[21] and can be used as a rapid surrogate for platelet measurement in the acute setting. Repletion of fibrinogen is generally guided by use of a fibrinogen-specific parameter (using reagent platelet inhibitors). TEG CFF MA of 12 mm or ROTEM FIBTEM MCF of 8 mm tends to correlate with a plasma fibrinogen concentration of 150 mg/dL as determined by the Clauss method.[44]

Due to space constraints, not all clinical areas with utility for VET have been included here. This includes use of VET for anticoagulation monitoring.

4.1 | Cardiac surgery

Cardiac surgeries present unique challenges to hemostatic management, due largely to the effect of the CPB circuit:

1. Activation of platelets, leading to reduction in platelet function[45]
2. Hemodilution
3. High dose heparin dosing

For all of these reasons, transfusion rates in cardiac surgery are very high, with 32%–46% of patients receiving blood products during bypass surgery.[46,47]

In the past 25 years, VET-guided transfusion algorithms after cardiac surgery have been assessed by seven RCT using TEG and seven using ROTEM.[48] In sum, the available literature shows that VET-based management algorithms may be beneficial in reducing transfusion of RBCs, plasma, and platelets, as well as postoperative blood loss 12 and 24 h after surgery, and variably for length of stay.[2,48–52] VET methods are also of benefit in assessing any residual heparinization following protamine reversal. VET use has not been shown to consistently improve mortality.[2,13,48,53,54] However, these conclusions are based primarily on lower quality RCTs with a high risk of bias. Karkouti et al from 2016 stands out as a large RCT showing a transfusion (but not mortality) benefit of VET, specifically ROTEM delta.[55]

VET also has utility in the post-operative setting for distinguishing postsurgical bleeding from coagulopathy.[56] However, this has not clearly translated to a decreased re-operation rate in patients managed under a VET-guided transfusion algorithm.[13]

Overall, VET likely increases the quality of cardiac surgical care by reducing blood product consumption without worsening patient outcomes.[8] It is a strong possibility that some of the benefit seen in these studies may be a result of VET implementation being paired with renewed efforts to standardize transfusion practice. As in other operative settings, use of transfusion algorithms alone reduces the transfusion of blood products.[54] An example of an algorithm provided by the Society for Cardiac Anesthesiologists is provided in Table 3.

TABLE 3 Example viscoelastic testing (VET)-guided transfusion algorithms.

	Platform implicated in guideline	Give plasma or 4-factor prothrombin complex concentrate (4F-PCC)	Give fibrinogen	Give platelets	Give TXA
Cardiac surgery Society of Cardiovascular Anesthesiologists, 2019[7]	ROTEM (likely delta)	EXTEM CT >100 s	EXTEM A10 < 40 mm AND FIBTEM A10 < 10 mm	EXTEM A10 < 40 mm AND FIBTEM A10 > 10 mm	INTEM or EXTEM ML >7% at 30 min OR INTEM or EXTEM ML >15% at 60 min
	TEG (likely 5000)	CKH R-time > 12 min	rTEG MA <40 mm AND CFF MA <8 mm	rTEG MA <40 mm AND CFF MA >8 mm	CK LY30 > 7.5%
Trauma surgery ACIT[37]	ROTEM delta	EXTEM CT >80 s AND EXTEM A5 ≥ 40 mm	FIBTEM A5 < 10 mm	(EXTEM A5 – FIBTEM A5) <30 mm	EXTEM LI30 < 85%
	TEG 5000	rTEG MA ≥65 mm AND rTEG ACT >120 s	CFF MA <20 mm	(rTEG MA – CFF MA) <45 mm	rTEG LY30 > 10%
Liver transplant[a] Adapted/modified from[38–40]	ROTEM delta	EXTEM CT >110 s	FIBTEM A10 ≤ 8 mm	EXTEM MCF <40 mm or A10 < 35 mm AND FIBTEM A10 or MCF >8 mm	EXTEM ML >15% AND APTEM decreases the CT or CFT >15% or increases the MCF >15% compared to EXTEM
	TEG 5000	CK R-time > 10 min, no significant correction with CKH	CFF MA ≤13 mm	CK MA <50 mm AND CFF MA >13 mm	CK LY30 > 10%
Post-partum hemorrhage[a] Adapted/modified from[41–43]	ROTEM delta	EXTEM CT >80 s	FIBTEM A5 < 7 mm or 7–12 mm with ongoing or high risk of hemorrhage	EXTEM MCF <45 mm AND FIBTEM normal	N/A
	TEG 6 s	CK R > 7.6 min	CFF A10 ≤ 17 mm	CRT MA <57 mm AND CFF A10 > 15 mm	N/A

Note: Guidance for the transfusion of plasma-rich blood products and the administration of antifibrinolytics is provided by threshold or trigger VET parameters. These algorithms are the product of expert consensus and are intended for use in specific and differing clinical settings; they do not replace informed medical decision making. Observational trial of Quantra in OLT (NCM04312958) has recently completed enrollment.

[a]There are no broadly applicable triggers/guidelines available for TEG or ROTEM-based management of liver transplantation or PPH. The cutoffs displayed reflect the citations as well as local practice.

TEG-PM can identify patients at increased risk of bleeding due to residual antiplatelet effect prior to surgery.[57] Other than PlateletMapping, studies have generally failed to show any benefit of preoperative VET in predicting operative bleeding, however.[8]

The Quantra platelet contribution to clot strength (PCS) parameter decreases significantly over the course of cardiopulmonary bypass[27] and is significantly associated with major bleeding even after correction for platelet count.[58] The Quantra PCS and TEG 5000 CK MA both similarly predicted clinical need for transfusion of platelets (area under the curve 0.71 and 0.70, respectively) but both performed poorly at predicting the need for plasma transfusion.[59]

In 200 adult cardiac surgical patients with ROTEM sigma collected immediately after heparin reversal, the mean sensitivity and specificity of FIBTEM A10 ≤ 8 mm for the identification of hypofibrinogenemia (<150 mg/dL) were 0.75 and 0.90, respectively, which are in a similar range to that reported in several previous studies using the ROTEM delta.[60] Quantra QPlus sensitivity and specificity for hypofibrinogenemia in a combined cardiac and orthopedic surgery dataset has been reported as 0.88 and 0.88, respectively.[28] Quantra results are available more quickly than ROTEM sigma.[61]

4.2 | Trauma

VET has emerged as an important tool for directing transfusion support for trauma-induced coagulopathy (TIC), in place of empiric or ratio-based management.[10,62] TIC is often defined by INR >1.2[37] and is thought to be due to uncontrolled release of tissue factor causing widespread thrombin activation, consumption of coagulation factors, and consumption/activation of platelets. Massive hemorrhage after trauma carries a hospital mortality rate of over 50% and, despite advances in resuscitation protocols, one in four trauma patients with severe bleeding still dies.[63]

Many observational studies have suggested a trend toward improvement in blood product use and mortality with the use of VET in trauma resuscitation.[49,64] VET offers reasonable accuracy for quickly identifying thrombocytopenia during traumatic bleeding[65] and the use of parameters reported early in the wavetrace formation (A5, A10 on ROTEM) may expedite recognition.[66] VET can also accurately assess the effect of fibrinogen concentrate administration.[67] However, prediction of need for plasma is less robust. Optimal CK R-time thresholds for diagnosing an INR over 1.5 and 2.0 were 3.9 and 4.3 min, respectively—these values are in the lower range of manufacturer normal range (4–8 min) for the TEG CK R time and showed <10% specificity.[5] One study showed that 44% of patients with exceptionally severe trauma (Injury Severity Score [ISS] >30) had normal TEG CK findings.[68]

Use of VET is now advised for initial evaluation in the current edition of the American College of Surgeons' Advanced Trauma Life Support (ATLS) recommendations.[9] A 2017 review by the Canadian Agency for Drugs and Technologies in Health found that while VET may be cost-effective in comparison to CCT in trauma patients according to a single economic analysis, a lack of evidence surrounding their clinical effectiveness limited their validity.[69] 2018 British Society of Haematology recommendations on trauma state that normal VET results confer a high negative predictive value for transfusion need, enabling the clinical team to monitor the patient closely without immediate activation of massive transfusion protocol (MTP).[10]

Two recent RCT have been published, which showed somewhat conflicting results:

1. Gonzalez et al.[70] randomized 111 adult trauma patients who met the criteria for activation of MTP to either a TEG-guided MTP algorithm or one guided by CCT, with a primary outcome of 28-day survival. The TEG-guided algorithm significantly improved survival compared with the CCT algorithm. This is despite patients randomized to TEG receiving significantly fewer plasma and platelet units in the first 2 h compared to the CCT group. Total transfusion at 24 h was not different between the groups. The CCT randomized group also had blinded TEG performed and results were not significantly different compared to the TEG randomized group.
2. In contrast, the iTACTIC multicenter trial[71] randomized 396 adult trauma patients who met the criteria for activation of MTP to VET (TEG or ROTEM) or CCT guided trauma resuscitation. The trial did not show an overall significant benefit to VET guided resuscitation in severe trauma. While there was no difference in total blood product use, the VET arm saw higher transfusion rates for platelets and fibrinogen supplementation. The traumatic brain injury (TBI) subgroup managed with VET had a significantly improved 28-day mortality.
    i. The iTACTIC trial utilized the ACIT (Activation of Coagulation and Inflammation in Trauma)-developed TEG- and ROTEM-based cutoffs to identify TIC and establish thresholds for blood product administration[37]; these are presented in Table 3.

Hyperfibrinolysis is the state of excessive activation of the fibrinolytic pathway. Hyperfibrinolysis is observed in trauma and can also be seen during liver transplantation, obstetrical hemorrhage, and iatrogenically following exogenous tPA administration. VET offers a unique benefit in the identification of hyperfibrinolysis; non-VET based fibrinolysis detection such as the euglobulin clot lysis time are generally not available with a turn-around time relevant to bleeding resuscitation. LY30/ML and plasma P-AP and tPA levels are positively correlated in trauma patients with hyperfibrinolysis.[72] VET-identified hyperfibrinolysis is seen in 2% to 5% of patients with major trauma but is associated with up to 80% early mortality.[49,73]

Many institutions now use VET for first-line assessment of hyperfibrinolysis. However, while the turn-around time is adequate, the diagnostic performance of VET in detection of clinically significant hyperfibrinolysis is not ideal. In Raza et al, EXTEM maximum lysis (ML) parameter could only detect hyperfibrinolysis in 5% of trauma patients; these patients had plasmin–antiplasmin (P-AP) complexes elevated to 30 times normal.[74] There are few comparative studies of

VET with other fibrinolysis detection methods, and an elevated LY30 (TEG) or reduced LI30 (ROTEM) parameter is neither sensitive nor completely specific for the condition. VET false positives for hyperfibrinolysis may be caused by clot retraction and/or slippage of the clot from the pin or walls of the cup in legacy testing methods. Use of aprotinin (ROTEM) or TXA (Quantra) can confirm hyperfibrinolysis in samples with increased clot lysis parameters.

Proposed cutoffs for identification of hyperfibrinolysis to guide antifibrinolytic treatment are included in the ACIT guidelines.[37] In contrast, British Society of Haematology guidelines recommend that antifibrinolytic therapy in trauma and obstetric patients not be withheld based on negative VET results.[10]

The flip-side of the coin from hyperfibrinolysis is fibrinolytic shutdown, or the reduction of fibrinolysis below the range typically seen in trauma/bleeding/operative patients.[72] Interpretation in the proper clinical context is crucial, as a total absence of clot lysis falls within reference ranges for healthy donors and high fibrinogen levels can reduce blood tPA sensitivity.

Fibrinolytic shutdown is the most prevalent phenotype found in severely injured trauma patients. These patients have lower incidences of massive transfusion and higher incidence of thrombosis and mortality attributed to multi-organ failure.[75] Patients with fibrinolytic shutdown nearly all still had increased P-AP complexes, implying that fibrinolysis was still occurring and that the reduced VET lysis detection reflected additional variables.[76] Patients with low LY30 but high D-dimers had greater injury severity and a higher incidence of severe head injury, multiorgan failure, and mortality than other groups. All endotheliopathy biomarkers were significantly higher in the low LY30/high D-dimer group, implying a link between ongoing endotheliopathy and fibrinolysis dysregulation that may drive multiorgan failure following trauma.[77]

4.3 | Cirrhosis and liver transplantation

Chronic liver failure is associated with reduced synthesis of hepatocyte derived procoagulant and anticoagulant factors as well as thrombocytopenia due to hypersplenism. Despite these abnormalities, patients with chronic liver failure are thought to have rebalanced hemostasis and generally have retained thrombin generation.[78] Cirrhotic patients with prolonged PT/INR and thrombocytopenia frequently show no significant functional evidence of coagulopathy on VET analysis.[79] Use of screening pre-procedure VET (rather than CCT) in patients with liver failure has been shown to reduce transfusions without increased risk of bleeding.[79,80]

Liver transplantation presents unique coagulation and transfusion challenges due to the dramatic changes seen during different phases of the operation. During the pre-explant phase, the hemostatic aberrations previously described in liver failure are present. During the anhepatic phase (after clamping of major vessels), no synthesis of coagulation factors occurs and circulating tPA is not cleared. During the neohepatic phase, there is an initial further release of tPA from the graft endothelial cells and platelet entrapment in the graft, with subsequent gradual normalization of hemostasis as the graft function improves. The evolution of these phases occurs quickly, in the span of minutes. Use of VET has become routine in liver transplantation with multiple small studies suggesting the benefit of VET-based transfusion algorithms to better predict bleeding compared to CCT[10] as well as to reduce the volume of transfused products, notably plasma and red blood cell units.[81] VET-based transfusion algorithms generally increase the transfusion of platelets and cryoprecipitate in this context.[38]

An RCT of ROTEM versus CCT in 81 liver transplantation patients showed that a VET-guided transfusion algorithm significantly reduced plasma and TXA use, increased fibrinogen supplementation, and had no effect on ICU re-admission or mortality.[39] Another RCT with 28 liver transplantations compared a TEG-based algorithm with CCT[40] and reported a reduction of plasma usage in the VET group but no difference in other blood products, intraoperative bleeding, length of stay, or mortality. ISTH guidelines state that VET can be used for hemostatic monitoring during liver transplantation, but do not provide a recommendation.[8]

Fibrinolysis is commonly identified in the anhepatic and early neohepatic phases of transplant, up to 36% of cases in one study.[82] The sensitivity of VET for hyperfibrinolysis in liver transplantation varies with instrument and reagent: lowest with kaolin-activated TEG (23.4% using LY30 > 8%) but increased with EXTEM and FIBTEM (46.1% and 94.4%, respectively, using ML >15%).[82]

There is also interest in use of VET during liver transplantation for identification of hypercoagulable states; VET may be useful in risk stratification of patients for thromboembolic complications following graft reperfusion such as hepatic artery thrombosis or pulmonary thromboembolism.

4.4 | Obstetrics

The hemostatic potential of the pregnant woman increases during the course of pregnancy due to estrogen-related physiologic adaptations thought to protect against hemorrhage. The plasma concentration of most procoagulant factors increases, most notably fibrinogen and von Willebrand factor.

Although the hypercoagulable state in pregnancy can be detected using CCT[83] as well as VET methods,[10,84,85] the latter offer a holistic assessment of hemostasis in order to guide decision-making in the face of conflicting or isolated abnormalities on CCT. A VET clot amplitude that is normal for the non-pregnant population may suggest a developing hypofibrinogenemia in a term woman. Therefore, the establishment of pregnancy-specific reference ranges in VET testing is best practice,[85] but is challenging and costly for hospital laboratories to determine.

While VET has no role in predicting post-partum hemorrhage (PPH) before it begins,[86] it has utility for rapid guidance of fibrinogen repletion during PPH. Hypofibrinogenemia has been shown to strongly predict the severity of bleeding during PPH and studies have affirmed the predictive value of a low FIBTEM MCF or CFF MA in this

setting.[10,87] The OBS2 randomized control study of women with moderate to severe PPH showed that a FIBTEM A5 > 12 mm indicated a fibrinogen level adequate for hemostasis.[88]

Use of VET-guided transfusion algorithms in PPH has been found to reduce blood product usage as well as complications including hysterectomy, ICU admission, and transfusion-associated circulatory overload.[41,42] One RCT of 54 parturients with PPH of more than 1500 mL, randomized to either ROTEM-guided or conventional support, showed significantly less plasma use and less blood loss in the ROTEM group.[89]

The role of VET to detect hyperfibrinolysis during PPH is unclear,[84,90] at least in part due to widespread use of TXA which has been shown to reduce bleeding-related mortality in this setting.[10,91]

4.5 | Identification of hypercoagulable states, including COVID-19

Hypercoagulability (relative to normal non-pregnant adults) can be detected with VET methods in many clinical settings, including in trauma, cancer, post-operatively generally, and in the third trimester of pregnancy and peripartum states. VET hypercoagulability is not well defined but generally refers to shortened clotting times and/or increased clot strength.

Clot stiffness, as assessed by MA/MCF/CS, has been found to predict post-operative thromboembolic complications.[92,93] In a secondary analysis of the PROPPR trial, patients who developed venous thromboembolism (VTE) following trauma exhibited more hypercoagulable TEG parameters and enhanced platelet function at admission relative to non-VTE patients, and were at higher risk for complications.[94] However, no single VET parameter is sensitive or specific in predicting thrombotic risks[8] and many severe congenital prothrombotic disorders are not detected.

Severe COVID-19 is associated with increased fibrinogen and D-dimers together with platelet activation (COVID-19 coagulopathy); these changes are associated with increased incidence of thrombosis. These changes were particularly widely seen during the initial waves of COVID-19. Meta-analyses of COVID-19 VET studies confirms the common finding of increased clot strength.[95] In a study of 141 COVID-19 patients, risk of death was significantly associated with increased EXTEM-MCF.[96] Use of VET to predict thromboembolism in COVID-19 has shown mixed results, however.[97,98]

Lysis indices are often quite low in COVID-19 patients and their blood often shows decreased responsiveness to exogenous tPA.[95,99,100] These findings are consistent with the elevated fibrinogen and PAI-1 levels seen in COVID-19.[100,101] COVID-19 ICU patients with LY30 of 0.0% and D-dimer >2600 ng/mL FEU had a venous thromboembolic event rate of 50% compared with 0% for patients with neither risk factor ($p = 0.008$).[102]

VET has seen adoption in the management of COVID patients requiring extracorporeal membrane oxygenation (ECMO)[103] due to its multidimensional data output and rapid turnaround. Use in this context demonstrated improved critical care outcomes and mortality due to COVID-19, in limited data sets. However, adoption patterns and treatment approaches remain non-standardized, varying between institutions, VET instruments, and ECMO types (V-V, V-A).

In January 2021, the FDA expanded the indication of previously approved VET systems to include hospitalized patients suspected of COVID-19 associated coagulopathy. The devices were also approved for use outside of clinical laboratories. This policy was intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services; that declaration is expected to expire on 5/11/2023.

5 | CONCLUSION

VET has become firmly established as part of the hemostatic assay armamentarium, especially in the perioperative setting. The capacity for real-time evaluation of multiple aspects of clotting offers the strongest benefits for VET over CCT methods, though the two types of testing are best regarded as complementary rather than totally overlapping. The advent of cartridge-based VET instruments has improved ease of use.

Over the last 10–20 years, exponential growth of literature on these testing methods has allowed for large-scale meta-analyses that have repeatedly demonstrated the benefit of VET in guiding transfusion of blood products, with nearly universal decreases in the volume and frequency of blood product transfusions suggesting more precise transfusion therapy and better patient blood management. A clear benefit to patient outcomes and overall mortality with VET has not been clearly demonstrated in most settings, however. VET has also become the most widely available means of assessing the fibrinolytic system, improving recognition and treatment of its disorders. VET also has some utility in the assessment of platelet function to predict patient bleeding,[104] though it underperforms compared to other platelet testing methods in predicting antiplatelet agent use.[32] VET has also recently become a method of interest in the management of patients with hemophilia[105] and other hematologic or autoimmune conditions.[14]

Overall, the available studies comparing VET instruments show imperfect agreements, particularly when results were outside the normal ranges. Therefore, the devices are not interchangeable and each device needs its own reference range and assessment of clinically relevant cut-off values and algorithms.

Given the current absence of widely-applicable cost-effectiveness data, institutions adopting VET must perform individual analyses to assess if the potential cost savings driven by improved transfusion practices adequately offsets the higher costs of VET. Such costs include annual service contracts, test reagents, quality control materials, quality assurance practices, and training.[49]

In summary, VET methods provide a rapid and holistic assessment of hemostasis in whole blood. Their use may drive better outcomes for patients and the blood supply, provided that VET interpretation is performed within the appropriate clinical context by informed medical personnel.

AUTHOR CONTRIBUTIONS

Geoffrey D. Wool and Timothy Carll planned, wrote, and edited the manuscript.

CONFLICT OF INTEREST STATEMENT

Timothy Carll reported no conflicts of interest. Geoffrey D. Wool is a member of advisory committees and receives honoraria from Diagnostica Stago and HemoSonics. He has received research funding from Siemens Healthineers.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Wool GD, Carll T. Viscoelastic testing: Critical appraisal of new methodologies and current literature. *Int J Lab Hematol*. 2023;1-16. doi:10.1111/ijlh.14144