

Multidisciplinary perspective on the use of viscoelastic tests in clinical practice (part 1)

Perspectiva multidisciplinaria del uso de test viscoelásticos en la práctica clínica (parte 1)

Sonia M.^a Veiras^{1a*}, Raquel Ferrandis^{2a}, Pilar Paniagua^{3a}, Azucena Pajares^{2a}, Rosa Beltrao^{4a}, Esther Méndez^{5a}, Gabriel J. Yanes^{6a}, M.^a Jesús Lorenzo^{7b}, Fco. Javier Lirón^{8b}, Ricardo Alonso^{9b}, Cecilia Cueto^{10b}, Noèlia Vilalta^{11c} y Marta Barquero^{12a}

¹Servicio de Anestesia, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela; ²Servicio de Anestesia, Hospital Universitario y Politécnico La Fe, Valencia; ³Servicio de Anestesia, Hospital de la Santa Creu i Sant Pau, Barcelona; ⁴Servicio de Anestesia, Complejo Hospitalario Clínico Universitario San Carlos, Madrid; ⁵Servicio de Anestesia, Hospital de Bellvitge, L'Hospitalet de Llobregat, Barcelona; ⁶Servicio de Anestesia, Hospital Virgen del Rocío, Sevilla; ⁷Área de Análisis Clínicos, Hospital Clínico Universitario de Vigo, Vigo; ⁸Área de Diagnóstico Biológico, Hospital Universitario la Ribera, Alzira, Valencia; ⁹Área de Análisis Clínicos, Hospital Universitario y Politécnico La Fe, Valencia; ¹⁰Área de Análisis Clínicos, Hospital 12 de Octubre, Madrid; ¹¹Unidad de Hemostasia y Trombosis, Servicio de Hematología, Hospital de la Santa Creu i Sant Pau, Barcelona; ¹²Unidad de Anestesiología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona. Spain

^aSociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor (SEDAR); ^bSociedad Española de Medicina de Laboratorio (SEMEDLAB);

^cSociedad Española de Trombosis y Hemostasia (SETH)

Abstract

Viscoelastic tests (VET) or point-of-care coagulation (POCC) devices are key tools in hemorrhage management, especially in surgery, but their use is expanding to other fields such as obstetrics, ECMO (extracorporeal membrane oxygenation) patients, and burn victims. While their role in cardiac surgery, polytrauma, and liver transplantation is more established, evidence regarding their impact on mortality remains controversial. One of the main limitations is the lack of result validation, as VETs are not comparable to standard coagulation tests, showing significant variability (up to 83% in ROTEM®). Additionally, quality control is not always managed by the laboratory, which may affect reliability. Anesthesiology, laboratory medicine, and hematology are involved in their interpretation. This document, supported by scientific societies from these specialties, aims to provide a comprehensive perspective on their functionality, scientific evidence, implementation, quality control, and potential economic benefits.

Keywords: Viscoelastic tests. Thromboelastography. Thromboelastometry. Consensus.

Resumen

Los test viscoelásticos (TVE) o point of care de coagulación (POCC) son herramientas clave en el manejo de la hemorragia, especialmente en cirugía, pero su uso se expande a otros ámbitos como obstetricia, pacientes en ECMO (oxigenación por membrana extracorpórea) y quemados. Aunque su papel en cirugía cardíaca, politraumatizados y trasplante hepático está más consolidado, la evidencia sobre su impacto en la mortalidad sigue siendo controvertida. Una de las principales limitaciones es la falta de validación de resultados, ya que los TVE no son comparables con los test estándar de coagulación, y muestran una variabilidad significativa (hasta el 83% en ROTEM®). Además, el control de calidad no siempre depende del laboratorio, lo que puede afectar su fiabilidad. Anestesiología, laboratorio y hematología participan en su interpretación. Este documento, respaldado por sus sociedades científicas, busca ofrecer una visión integral sobre su funcionamiento, evidencia, implementación, control de calidad y posibles beneficios económicos.

Palabras clave: Test viscoelásticos. Tromboelastografía. Tromboelastometría. Consenso.

*Correspondence:

Sonia M.^a Veiras
E-mail: veiras1@gmail.com

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Introduction

Viscoelastic tests (VETs) or point-of-care coagulation (POCC) tests have become important tools in hemorrhage management in various settings.

While surgical patients have been the primary beneficiaries of VET-guided management, an increasing number of non-surgical scenarios can also benefit from these devices.

In some settings, the use of VETs appears well-established. Specifically, cardiac surgery, polytrauma care, and liver transplantation are procedures where VETs have been firmly established as guides for hemostatic correction therapy. There are other specialties where these POCC devices are not yet established, but scientific literature opens new avenues for their use, such as in obstetrics, burns, patients on ECMO (extracorporeal membrane oxygenation), etc.

The reality is that even in settings where VETs seem most consolidated, the scientific evidence is controversial, and robust conclusions regarding reductions in mortality or improvements in clinical outcomes remain elusive in patients whose hemostasis has been guided by objectives derived from POCC device results.

There is an apparent lack of result validation, partly because VETs are not comparable to standard coagulation tests. Although the coefficient of variation (a measure of precision and internal quality control for an assay) is 5% for standard laboratory tests, it reaches 39% for thromboelastography (TEG) and up to 83% for thromboelastometry (ROTEM®).

Quality control of VETs in many centers is external to the laboratory service and is performed by the regular users of the device, but this fact can also reduce the reliability of the results.

The clinical use and interpretation of VET results involves collaboration among various medical specialties, specifically anesthesiology, laboratory, and hematology. Scientific societies from these three specialties have collaborated on this document to present a global perspective on these devices and to convey the most up-to-date information on their basic operating principles, scientific evidence for their use in various clinical scenarios, different implementation models, quality control, and cost savings, among other aspects.

Purpose of the document

- To jointly present, on behalf of the three scientific societies, the clinical relevance and utility of POCCs

as a hemostatic management measure in bleeding patients.

- To reach a consensus on the best way to perform these tests, so that we can reduce their analytical variation, expressed as the coefficient of variation in their results, and thus provide robustness to them.
- To examine the economic suitability of using these devices in relation to the savings in blood products and earlier control of hemorrhagic events.

Document recipients

Physicians from different specialties who manage or wish to manage these VETs as part of their therapeutic arsenal, i.e., therapeutic and diagnostic.

Description of available VETs on the market. Operating principles

Fundamentals of VETs

These devices offer a more physiologically accurate assessment of coagulation than conventional laboratory tests. These tests provide dynamic and global information on the viscoelastic properties of blood by integrating platelets, coagulation cascade components, and cellular blood elements. Basically, the assays involve inducing *in vitro* coagulation of the patient's sample with different reagents that activate the intrinsic or extrinsic pathway and reflect the clot characteristics. There are various analyzers for performing viscoelastic tests, which, through different technologies, offer results in the form of graphs and parameters with numerical data informing about clot quality (Table 1).

Although the available analyzers could be considered to aim for the same objective, they present differences among themselves. Table 2 illustrates the main advantages and disadvantages of each.

Thromboelastography TEG® 5000

The principle of the rotational thromboelastography technique of the TEG® 5000 (Haemonetics) consists of inducing *in vitro* coagulation of a blood sample (360 µL) from the patient in a small cuvette that rotates with uniform and constant motion. The disposable cuvette, maintained at 37°C, rotates alternately (4° 75' every 5 s) around a small fixed shaft or piston. As blood clots, resistance from the clot increases, and these variations are recorded by an electromagnetic transducer, which converts them into an electrical signal that

Table 1. Point-of-care coagulation devices available on the market

Analyzer	Company	Technology	Presentation
TEG® 5000	Haemonetics	Rotational thromboelastography	Independent liquid reagents
ROTEM® Delta	Instrumentation laboratory (Werfen)	Rotational thromboelastometry	Independent liquid reagents
ROTEM® Sigma	Instrumentation laboratory (Werfen)	Rotational thromboelastometry	Cartridge tests
ClotPro®	Enicor GmbH (Haemonetics)	Rotational thromboelastometry	Lyophilized reagents preloaded in tips
TEG® 6S	Haemonetics	Harmonic resonance	Cartridge tests
Quantra®	Hemosonics (Stago)	Sonorheometry (SEER)	Cartridge tests
Sonoclot®	Sienco Inc.	Microviscometry	Independent liquid reagents

Table 2. Advantages and disadvantages of different devices

Test	Advantages	Disadvantages
Individual Tests ROTEM® Delta ClotPro® Sonoclot®	Smaller sample volume Valid for low sample volume (paediatric) Allows selection of test based on algorithm; more affordable	Greater ariability due to manual sample pipetting Requires more user training
Cartridge Tests ROTEM® Sigma TEG® 6S Quantra®	Easier sample processing Less need for expert personnel Lower pre-analytical ariability	Larger sample volume (except TEG® 6S) Not valid for low sample volume (paediatric); more expensive

the analyzer's software translates into a graph and numerical results (Fig. 1). The recorded variations depend on both the kinetics and the characteristics of the clot¹⁻³.

The analyzer has two independent channels and liquid reagents for performing the tests. The available parameters and tests are found in tables 3, 4, and 5.

In April 2023, a change was made to the FIBTEM C reagent contained in ROTEM® Sigma Complete and Sigma Complete + Heparin cartridges. The formulation was improved with the addition of tirofiban to the already existing cytochalasin D, both platelet inhibitors, thereby achieving almost total elimination of platelets in the FIBTEM C test. The aim of the new formulation was to address a problem with samples having high platelet levels.

In 2024, a Welsh working group observed a decrease in FIBTEM C A5 cutoff values (1-2 mm) in obstetric patients compared to previous cartridge batches (IVDD) following the test improvement with the addition of tirofiban. This means that clinical decision algorithms might require adjustment to avoid inappropriate (additional) fibrinogen concentrate transfusions. However,

evidence only exists at a single center, and it remains to be seen whether this modification also affects other scenarios (cardiac surgery, liver transplantation, or traumatology).

Rotational thromboelastometry (ROTEM® Delta)

Rotational thromboelastometry ROTEM® has a very similar principle to TEG. Its technology is based on the disposable cuvette, which is maintained at 37°C and on which the patient's citrated whole blood (330 µL) is deposited, remaining fixed, while the vertical shaft or piston introduced into the sample oscillates (4° 75' every 6 s). The movement is detected by an optical system located at the upper end, whose data are transferred and processed by the analyzer's specific software⁴. When the sample coagulates, the resistance to the piston's rotation changes, reducing the rotation amplitude of the shaft, and these data are recorded and interpreted by the analyzer, transforming them into a graph with their values, which depend on the kinetics and characteristics of the clot (Fig. 2).

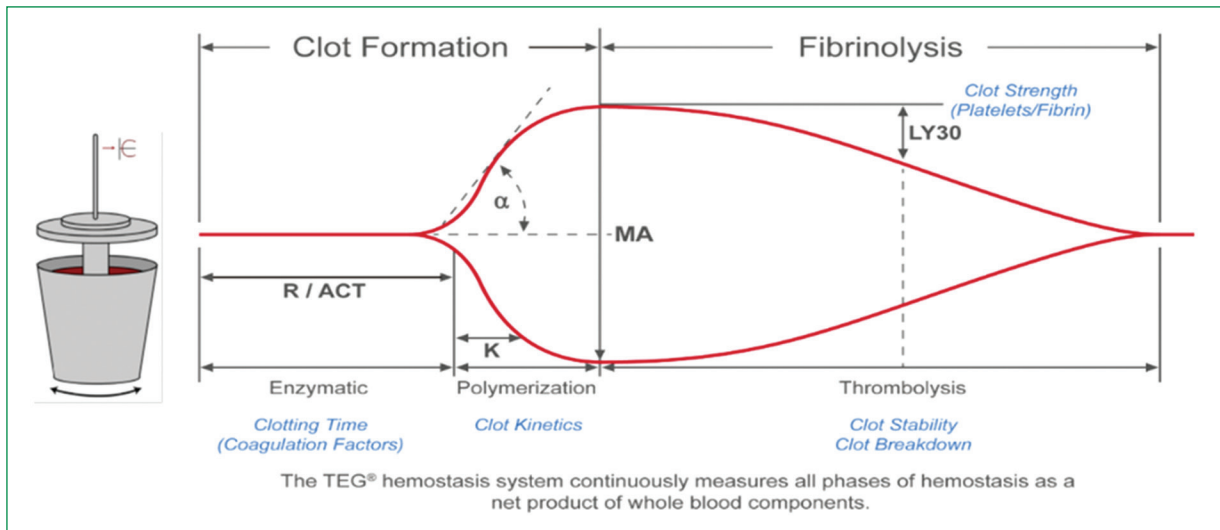


Figure 1. Phases and parameters of clot formation in the TEG system (courtesy of Ferrer, Haemonetics Corp.¹).

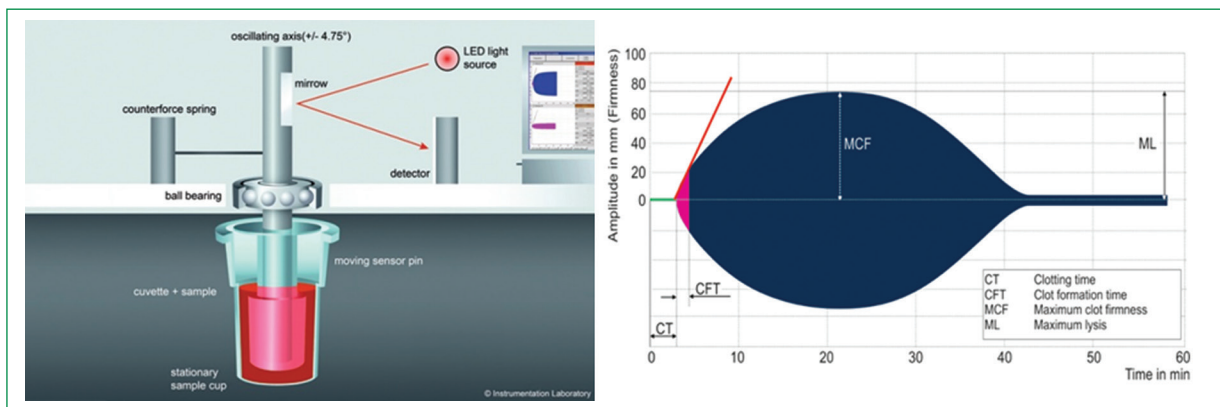


Figure 2. Diagram of the ROTEM system's operation (courtesy of Werfen⁴).

The Delta model has 4 independent channels and liquid reagents for performing five different tests that can be processed independently and according to algorithms or indications^{2,3,5}. Parameters and tests are available in tables 3, 4, and 5.

Rotational thromboelastometry (ROTEM® Sigma)

This system is primarily designed for point-of-care testing (POCT). It is based on cartridge technology, is a closed system, easy to use, and fully automated; no pipetting or test preparation is necessary. The tube containing the citrated whole blood sample is directly punctured into the cartridge, which is then inserted into the analyzer (Fig. 3). Each cartridge contains

chambers/wells with the necessary reagents to perform the different tests. Results are expressed in graphs and numerical data similar to the ROTEM® Delta.

Parameters and available tests with their description can be found in tables 3, 4, and 5.

ClotPro® system thromboelastometry

The ClotPro® system^{1,6} is a 6-channel viscoelastometry analyzer that uses elastic motion thrombelastography, an improved next-generation viscoelastometry technique. Similar to conventional rotational thromboelastometry systems, the cup and pin surfaces experience a relative movement of about 5° driven by an elastic element. In the ClotPro® analyzer, the cup rotates while the pin remains stationary. The cup's rotation

Table 3. Parameters of different viscoelastic test analyzers

Parameter description	TEG® 5000	ROTEM® Delta & Sigma	ClotPro® System	TEG® 6S	Quantra®	Description
Reaction/Clotting time	R/ACT (s)	CT (s)	CT (s)	R/ACT (s)	CT (s)	Parameters for assessing clot formation (coagulation factors and anticoagulants)
Clot formation time	K (s)	CFT (s)	CFT (s)	K (mm)	-	
Clotting time with heparinase	-	-	-	-	CTH (s)	
Clotting time ratio	-	-	-	-	CTR	
Clot strength. Amplitude at various times (5, 10, and 20 minutes)	A10 (mm)	A5, A10, A20	A5, A10, A20	A10 (mm)	-	Parameters for assessing clot firmness
Fibrinogen contribution to clot strength	-	-	-	-	FCS (hPa)	
Platelet contribution to clot strength	-	-	-	-	PCS (hPa)	
Maximum clot firmness	MA (mm)	MCF (mm)	MCF (mm)	MA (mm)	CS (hPa)	
Clot lysis stability. Lysis at 30 minutes	LY30 (%)	LY30 (mm)	LY30 (mm)	LY30 (mm)	-	Parameters for assessing clot stability and/or fibrinolysis
Clot stability. Maximum lysis	ML	ML	ML	-	CSL (%)	

A5: clot amplitude at 5 minutes; A10: amplitude at 10 minutes; A20: amplitude at 20 minutes; CFT: clotting firmness time; CS: clot stiffness; CT: clotting time; LY: lysis; FCS: fibrinogen contribution to clot stiffness; CSL: clot stability to lysis; K (K-time): clot formation time; MA: maximum clot firmness in TEG; MCF: maximum clot firmness in ROTEM; PCS: platelet contribution to clot stiffness; R/ACT: activated clotting time result.

Table 4. Cartridges and tests available on TEG® 6S, ROTEM® Sigma, and Quantra®

Analyzer	Cartridge	Test	Description
ROTEM® Sigma	Rotem Sigma Complete	EXTEM	Rapid assessment of clot formation, fibrin polymerization, and fibrinolysis via extrinsic and intrinsic pathways
		INTEM	Qualitative evaluation of fibrinogen status
		FIBTEM	Differentiates between hyperfibrinolysis and platelet-mediated clot retraction/FXIII deficiency
		APTEM	Particularly suitable for patients requiring fibrinolysis diagnosis
	Rotem Sigma Complete+Hep	EXTEM	Rapid assessment of clot formation and fibrin polymerization via extrinsic and intrinsic pathways
		INTEM	Qualitative evaluation of fibrinogen status
		FIBTEM	Differentiates between factor deficiency and heparin effect
		HEPTEM	Recommended for patients on therapeutic heparin and endogenous heparin (heparinoids)
TEG® 6S	Global Hemostasis Cartridge	Kaolin test Kaolin TEG with Heparinase RapidTEG™ Functional Fibrinogen TEG	Provides a global assessment of patient hemostasis Qualitative evaluation of fibrinogen status Differentiates between factor deficiency and heparin effect
	PlateletMapping® Cartridge	PlateletMapping®	Assesses platelet activity by studying its aggregation capacity
Quantra®	QPlus Cartridge		Evaluates clot formation, the contribution of fibrinogen and platelets to clot firmness, and the influence of heparin Recommended for cardiovascular and orthopedic surgery
	QStat Cartridge		Includes tests to evaluate clot characteristics and lysis via intrinsic and extrinsic pathways, and includes a test with tranexamic acid Indicated for intensive care, traumatology, and liver transplantation

Table 5. Tests available for TEG® 5000, ROTEM® Delta, and ClotPro®

TEG® 5000	ROTEM® Delta & Sigma	ClotPro® system	Description
-	Extem	Ex-Test	Rapid coagulation assessment, activating the extrinsic pathway with recombinant tissue factor
Kaolin TEG	Intem	In-Test	Evaluates the intrinsic pathway by activating it with Kaolin or ellagic acid
Functional Fibrinogen TEG	FIBTEM	Fib-Test	Evaluates the contribution of fibrin and platelets to clot firmness. Eliminates platelet participation through a GPIIb/IIIa antagonist inhibitor and/or cytochalasin D
Kaolin TEG with Heparinase	Heptem	Hi-Test	Evaluates the presence of heparin or synthetic heparinoids in the sample by the action of heparinase
-	Aptem	Ap-Test	Evaluates fibrinolysis using aprotinin as a direct plasmin antagonist
RapidTEG™	-	-	Assay to rapidly evaluate coagulation properties by activating the intrinsic pathway with Kaolin and the extrinsic pathway with tissue factor
-	-	RVV-Test	Screening test to detect direct factor Xa anticoagulants. Uses Russell's viper venom as a direct FX activator
-	-	ECA-Test	Screening test to detect direct factor II (thrombin) anticoagulants. Uses ecarin as a prothrombin activator
-	-	TPA-Test	Allows assessment of patient antifibrinolytic therapy. For this, it induces fibrinolysis using recombinant tissue plasminogen activator
TEG PlateletMapping®	-	-	Evaluates platelet inhibition/aggregation



Figure 3. Example of a cartridge for the ROTEM® Sigma (courtesy of Werfen®).

is detected by an electronic sensor sensitive to changes in rotation. During clot formation, the movement between the cup and the pin decreases as clot resistance increases. This data is recorded by the analyzer, which interprets it in the form of graphs and numerical results (Fig. 4).

Reagents for each assay come lyophilized and preloaded in pipette tips. The citrated blood sample is pipetted with these tips (340 µL), allowing for simple and safe mixing with the reagent. The analyzer has six independent channels and nine different tests whose reagents are preloaded in pipette tips for independent performance.

Currently, only the ClotPro® system has specific screening tests for the detection of direct oral anticoagulants (DOACs) that are antagonists of coagulation factor X (FX) (apixaban, rivaroxaban, edoxaban) and thrombin (FII) (dabigatran)^(a,b). They show high sensitivity and specificity for detecting DOACs, which is very useful in emergency situations.^{7,8} The available parameters and tests with their descriptions can be found in tables 3, 4, and 5.

TEG® 6S thromboelastogram

The TEG® 6S system (Haemonetics)¹ uniquely employs harmonic resonance technology, assessing the physical properties of the clot using sound waves, such that clot formation is accompanied by changes in resonance frequency. To measure clot strength with the resonance method, the sample is exposed to a fixed vibration frequency. As the sample transitions from a liquid state to a gel-like consistency during coagulation, the elastic modulus and resonance frequency increase. Resonance frequency increases over time and with clot firmness. This analyzer uses a cartridge system containing the necessary reagents for the tests; it is a closed and fully

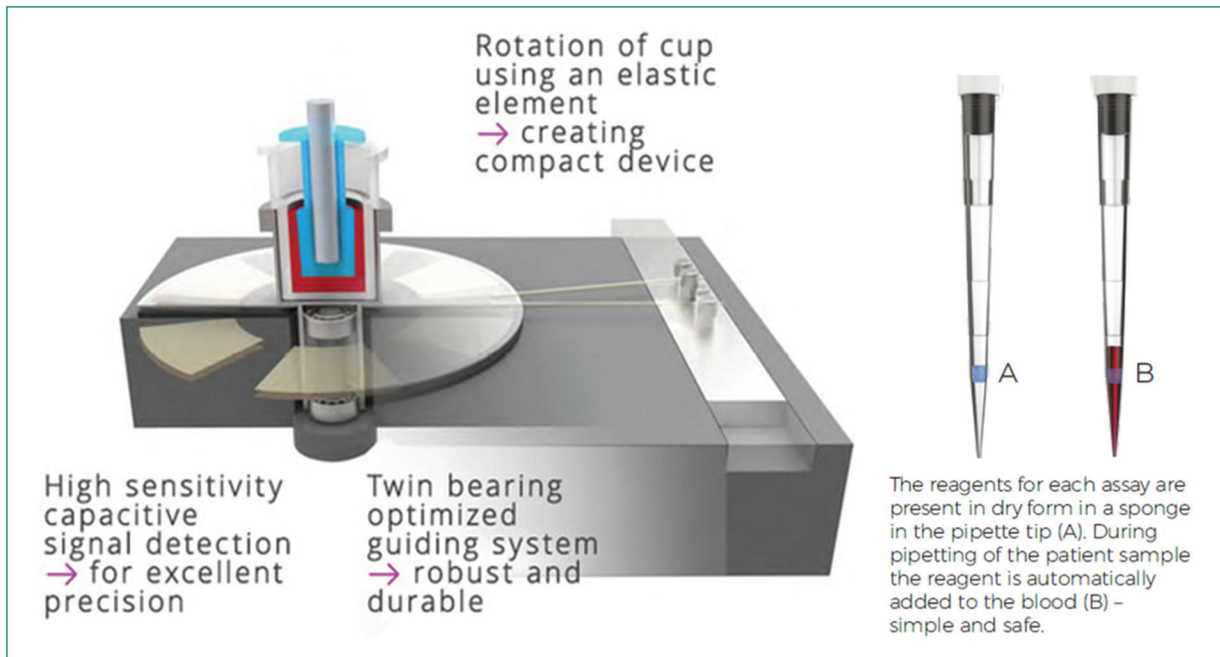


Figure 4. Diagram of the ClotPro® system's operation and tips with preloaded reagent (courtesy of Ferrer, Haemonetics Corp.¹).

automated system. Four hundred μL of whole blood are directly pipetted into the cartridge. In the wells/chambers of the cartridge, the clot forms and is subjected to sound waves. The analyzer displays the results in the form of graphs and numerical values (Fig. 5).

The available parameters and tests with their descriptions can be found in tables 3, 4, and 5.

Quantra® system

The Quantra® system (Hemosonics) is based on a technology called SEER sonorheometry⁹⁻¹² (sonic estimation of elasticity via resonance). It uses ultrasound technology to measure changes in the viscoelasticity of the sample. This technology measures clot elasticity at time intervals using ultrasound, and the evolution of elasticity is represented in a graph expressed in hectopascals/minute (hPa/min). By measuring elasticity, the PCS parameter (platelet contribution to clot stiffness) is obtained, which is related to the number and function of platelets. This fully automated system is designed for ease of use in POCT; it uses a cartridge system, is easy to use, and fully automated. The tube with the citrated whole blood sample is directly punctured into the cartridge. The sample is subjected to ultrasound pulses that generate data interpreted by the analyzer and displayed in the form of dials and large numerals (Fig. 6).

Sonoclot® sienco

This analyzer is described as a microviscosimeter.¹³ The electronic components are sensitive to any resistance to the movement of the oscillating probe within the blood sample. The higher the fluid viscosity, the greater the output signal generated by the analyzer. The output signal is calibrated according to reference viscosity standards and is reported in normalized "clot signal" units. The analyzer displays a graph representing the different phases in clot formation, from coagulation activation, through fibrin formation and clot retraction, to the formation of a mature clot (Fig. 7).

Different tests are available for the Sonoclot® model that allow evaluation of clot formation, heparin anticoagulation control, and platelet function. Currently, this analyzer is not marketed in our country.

Analytical considerations and implementation modes of VETs

Pre-analytical phase

Suitable containers for these types of tests are tubes with 3.2% sodium citrate as an anticoagulant (blue cap). Although some analyzers can use whole blood without anticoagulant, this is not recommended due to the possibility of sample coagulation. To prevent

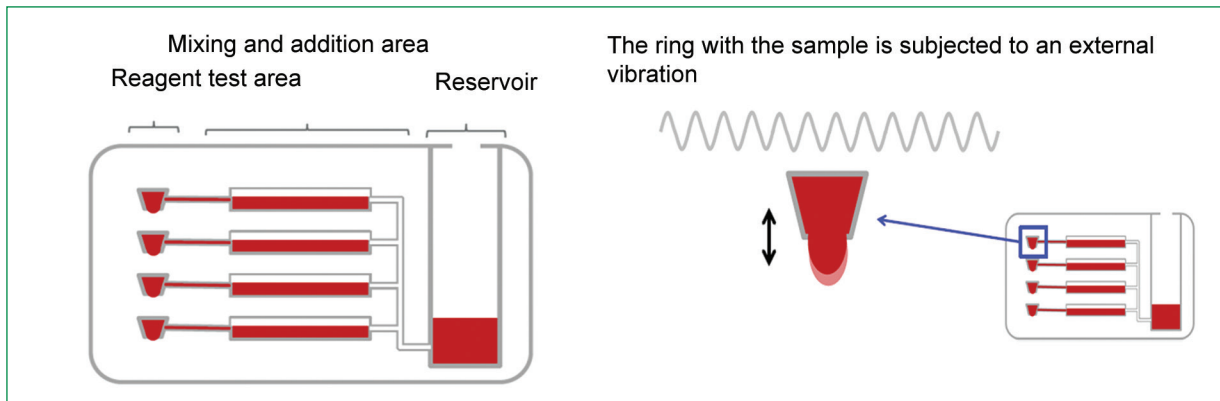


Figure 5. Diagram of the cards and operation of the TEG® 6S system (courtesy of Ferrer, Haemonetics Corp.¹⁾).

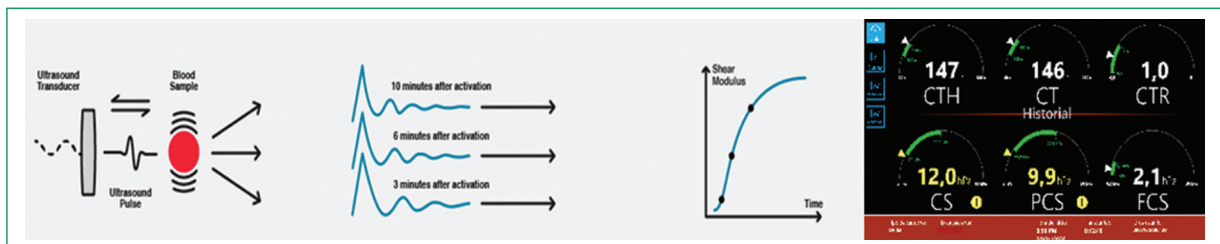


Figure 6. Diagram of sonorheometry technology (SEER, sonic estimation of elasticity via resonance) (courtesy of Biometra⁹).

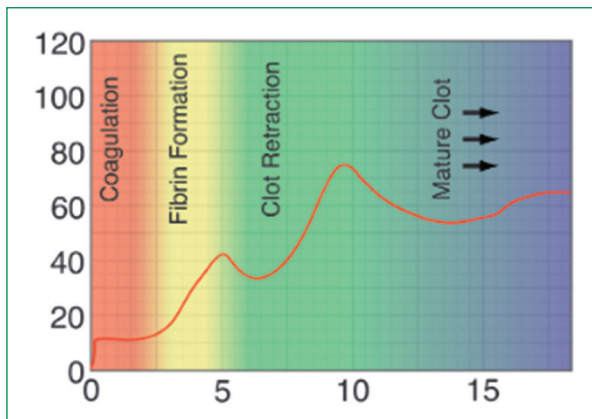


Figure 7. Hemostatic phases of the Sonoclot® Sienco (taken from Sienco Home¹³).

sample dilution by the anticoagulant, it is recommended that tubes be filled to their maximum capacity recommended by the manufacturer.

Once the sample has been drawn, the tube must be processed within 4 hours of collection. There are no recommendations for sample resting time. For ROTEM, sample processing is recommended between 30^{14,15} and

120 minutes¹⁶ after collection. Refrigeration or freezing is not advised. Other authors recommend that samples be analyzed immediately,¹⁷⁻¹⁹ which is consistent with the immediacy of clinical actions derived from the results.

Since these types of tests are sensitive to small variations, both analytical and biological, centers are recommended to take appropriate measures to reduce variation in their measurements.

Skill is required to detect subtle variations in results obtained with patient samples, but for this, errors made in sample collection, preparation, handling, and analysis that might mask these physiological variations must be minimized.

Despite this pre-analytical variability, some studies encourage users of viscoelastic tests to use evidence-based guidelines developed for these assays²⁰ to minimize sources of variation and, therefore, maximize the diagnostic utility of these methods.

PRE-ANALYTICAL RECOMMENDATIONS THAT SHOULD BE TAKEN INTO CONSIDERATION

– Avoid sample hemodilution from line drawing.

- Fill the citrate tube to the recommended level to prevent hemodilution by the liquid anticoagulant (citrate).
- Homogenize the drawn sample to prevent coagulation.
- Perform tests as soon as possible, whether performed as POCT or sent to the emergency laboratory.
- If determinations are requested from the emergency laboratory, it is recommended to establish a consensual protocol between departments to expedite the process.
- Reference ranges for each test should be evaluated and adapted to the reference population.

Quality control

Internal quality control is a procedure used to detect, reduce, and correct possible analytical deficiencies before issuing a result, thereby ensuring the necessary provision to meet the clinical requirements for which the analyzer is intended. Its objective is to validate calibration and/or measurement processes and thus detect random errors that may affect results during the measurement process and obtain periodic statistical calculations of analytical imprecision²¹ for evaluation. For this purpose, a validated material is used, and if possible, with a matrix most similar to the biological system containing the constituents to be measured, which is usually supplied by the same commercial company as the analyzer.

Some analyzers use electronic quality control that, upon analyzer power-on or on demand, checks all electronic actions involved in the measurement process. This procedure is complementary and cannot replace classic quality control, which uses biological material simulating the sample.

In the case of POCT tests, there is no consensus on the frequency with which internal quality control should be analyzed. This frequency will depend on the importance of detecting measurement errors and the repercussions these may entail. Recommendations exist to do it from each work session (8 h)²² to weekly²³ or monthly, but also with each change of reagent lot and each opening of a new reagent box. Manufacturers of thromboelastography equipment recommend daily use of electronic controls and performing conventional quality control with validated material monthly for equipment with little use, or more frequently if the equipment is used more often.

For ROTEM and ClotPro® models, internal quality control²³ is recommended weekly, and for Sonoclot®,

a daily viscosity test and classic plasma quality control monthly are recommended. These are minimum recommendations, and it is advised that each center's multidisciplinary working group in charge of VETs establishes a frequency protocol for quality control analysis that ensures the perfect functioning of the analyzers based on their volume and frequency of work.

External quality control is known as an intercomparison program and involves comparing the results obtained by our center with the rest of the centers participating in the program to detect total error and bias of analytical procedures.²⁴

In this type of program, the control sample must be blind, i.e., of unknown value to the center at the time of analysis, and it may be appropriate to use a set of control samples with different values.

Currently, there are several options for external quality assessment programs for VETs. In the United Kingdom, the National External Quality Assurance Scheme (NEQAS, <https://ukneqas.org.uk>) has an intercomparison program for TEG® 5000 and ROTEM® Delta analyzers. This program uses lyophilized plasma samples.

Recently, this program has included cartridge-based analyzers, such as the TEG® 6S and ROTEM® Sigma. Other external quality assessment programs for these types of tests are the External Quality Control of Diagnostic Assays and Tests (ECAT) (<https://www.ecat.nl>) in the Netherlands and WEQAS (<https://www.weqas.com/services/poct-eqa/viscoelastic-haemostasis/>), all using lyophilized plasma as a sample.

As with any measurement of biological variables, both the management of internal quality control and participation in external quality programs are fundamental to demonstrating the validity and applicability/reliability of the results, and this applies to results obtained with VETs. It is recommended that all quality control records and records of actions taken with their results be kept for a minimum period of two years for consultation and possible audits.

QUALITY CONTROL RECOMMENDATIONS

- Perform internal quality controls at least with the frequency recommended by the manufacturer. At least one weekly control is advised.
- It would be advisable to participate in an external quality program that allows for intercomparison and accuracy of results.

- It is advised that the laboratory, as an expert in the management and evaluation of analytical control programs, be responsible for the management of quality controls, through the POCT coordinator, if a hospital POCT committee exists, or by laboratory personnel designated for this purpose. For traceability and record-keeping, as indicated by the POCT system implementation guidelines,²⁵ it is advisable to establish an IT connection with POCT management systems and/or the laboratory's IT system for patient registration and quality control, and through them with the IT system that manages the hospital's health records for viewing and consulting results.

Precision and accuracy of results

Results obtained in external quality assessment programs (NEQAS)²⁶ show very large coefficients of variation (CV), both for pipetting-based instruments, such as the ROTEM® Delta (CV range depending on parameter 7.2%-73.2%) and TEG® 5000 (CV range depending on parameter 17.4%-59.5%), and for cartridge-based instruments, such as the ROTEM® Sigma (CV range depending on parameter 3.9%-22.9%) and TEG® 6S (CV range depending on parameter 13.6%-30.7%). This wide variation may be for 2 reasons. The first is a pre-analytical factor related to the variability introduced by user manipulation. Vials are supplied lyophilized and must be reconstituted by the user. The skill and accuracy of pipetting can affect the final result.²⁷

This argument is reinforced by observing that instruments with cartridge technology, where there is no pipetting by the operator, have lower CV than those that do. But even so, sample handling remains important for all devices. This type of variability can also be transferred to the analysis of patient samples, highlighting the importance of the pre-analytical phase in performing these types of tests, emphasizing the crucial role of training and acquiring expertise with the materials used by the personnel who will perform the measurements on patients.

The second reason may lie in the use of lyophilized plasma samples in these intercomparison programs, instead of whole blood, as the devices are not designed to evaluate plasma. Currently, no provider of external quality programs can provide "fresh whole blood" or similar material as samples within their programs. In summary, lyophilized samples can be used to demonstrate test precision and allow peer comparison between different centers but cannot be used to guarantee accuracy.²⁸

Reference intervals

VETs are poorly standardized. Reports demonstrate the non-interchangeability of results obtained with thromboelastographic techniques and those obtained with thromboelastometry.²⁹

In addition to the reference intervals provided by manufacturers, no consensual reference values have been published. As with any laboratory test, centers should determine their own reference values, based on the characteristics of their local population. This is particularly difficult in the paediatric population. Some authors have established reference values for this type of patient for ROTEM® Delta⁴ and for TEG® 5000.³⁰

Implementation model of VETs

Obtaining rapid results for urgent clinical decision-making that allow early recognition of critical situations, faster therapeutic intervention, or reduction of perior postoperative complications are some important objectives of POCT.

VETs, due to their nature and immediate clinical application, are tests susceptible to being performed at the patient's bedside; however, they have always had certain limitations that have conditioned their use to relatively reduced clinical environments.

Pipetting of the sample and reagents, the relatively complex interpretation of results, and even the size and weight of the equipment, have posed significant barriers when implementing this technology at the patient's bedside in certain clinical units.

In search for the clinical utility of this methodology, diagnostic companies have implemented important developments in their devices that have allowed them to overcome the main obstacles and bring this technology to increasingly complex clinical environments, adapting to the clinical-care and organizational needs of different centers.

The use of VET at the point of patient care (POCT) provides speed and immediacy in performing the test and visualizing the results at the same location as the patient, thus reducing response and action times in a critical bleeding situation. However, it also exposes the procedure to a multitude of factors that can adversely affect sample analysis: the handling of analyzers by multiple, potentially unqualified operators, limited pre-analytical knowledge, and inadequate quality control management.²⁵

On the other hand, there is the centralized model, where VETs are performed in the emergency

laboratory, which has been implemented in many hospitals. This model offers a series of advantages: service available to the entire hospital, managed quality control, avoidance of interference from the movement of vibration-sensitive equipment (moving analyzers with carts from one place to another), and specialization of personnel performing the technique and inclusion in the patient's clinical history (this can also be done in POCT). The visualization of results is done remotely and in real time electronically and can be viewed simultaneously across different workstations or locations. This model involves perfect coordination between services, establishing consensual work protocols that allow reducing the time to obtain results, which is its main disadvantage.

In other hospitals, a mixed model has been chosen, with some analyzers in high-activity units (POCT) and other analyzers in the emergency laboratory, serving as support and service to the entire hospital. Therefore, each hospital center must implement the model that best suits its needs, advising that this implementation always be carried out with the control and management of a hospital POCT committee.

Description and current scientific evidence on the use of platelet function tests. Description of existing tests. Mapping using ROTEM®, TEG®, and Quantra®

In the context of coagulopathy, evaluating the contribution of platelets to hemostasis is fundamental. The role of platelets in primary hemostasis for clot generation, providing a surface for prothrombin-to-thrombin conversion, and catalyzing processes in secondary hemostasis, stabilizing the clot through fibrin mesh formation and improving clot firmness through clot contraction, thereby also restoring blood circulation, is well-known. There are various methods for evaluating platelet actions such as adhesion, aggregation, secretion, clot retraction, platelet morphology evaluation, etc. In clinical practice, platelet counts are frequently performed, but the evaluation of their functionality is less common. The difficulty of functional evaluation lies in the tests' ability to recreate the complex interactions that occur *in vivo* with the interaction of various mediators and the dynamic flow and shear conditions to which platelets are subjected. It should be noted that it is assumed before the test that platelets are inactive and will be activated after agonist exposure; however, at the time of the test, they may have already been

activated and apparently show impaired function in the *ex vivo* test.³¹ Bedside devices for diagnosing hemostatic status allow for targeted and early treatment, as well as avoiding unnecessary transfusions, by reducing response time compared to central laboratory analyses. Platelet count is used in the decision for platelet transfusion in this context; however, it has the limitation of delayed results from the central laboratory and does not detect functional defects that may be present despite normal counts. Various systems allow their use at the patient's bedside for functional assessment of platelet function in addition to counting, thus reducing diagnosis and treatment time.

Various systems are used for the evaluation of platelet function. Some are based on platelet aggregation, such as light transmission aggregometry (LTA), VerifyNow, or Plateletworks; others are based on platelet adhesion due to shear stress, such as PFA or the Impact-R system; others on flow cytometry analysis; others on the evaluation of thromboxane metabolites; and finally, those based on combined methods with global clot formation VETs. The main characteristics are shown in [table 6](#).

Not all can be used in the bleeding setting and they also vary depending on the need for processing. They are influenced by platelet count, although there is the possibility of analyzing platelet function with methods adjusted to the existing count.³² Overall, they are based on exposing the platelet to an agonist such as collagen, arachidonic acid (AA), epinephrine, adenosine diphosphate (ADP), thrombin, or thrombin receptor activating peptide or other activators of different pathways. That is, a limited number of platelet activation pathways can be explored simultaneously.

As a general rule, whenever a platelet function test is to be performed, pre-analytical platelet activation must be avoided, and for this, certain precautions are necessary in relation to the patient and the extraction technique. There are patient-related factors such as prior exercise, certain foods and supplements, coffee consumption, drugs such as non-steroidal anti-inflammatory drugs, or circadian rhythm. The extraction should be performed gently, with the minimum necessary tourniquet pressure and needles > 19 G with short connection tubes. Additionally, it is recommended to discard the first milliliters of the extraction to avoid activating substances due to endothelial injury. The type of anticoagulant used is also important, with citrate showing lower values of platelet aggregation,³³ and for transport, it is recommended to avoid pneumatic systems and to transport tubes in an upright position, avoiding agitation.

Table 6. Main characteristics of systems for platelet function evaluation

Test	Method	Advantages	Disadvantages	Notes
LTA	Aggregation measured by photo-optical transmission. Citrated sample or PRP	Identifies specific deficiencies, whether genetic or due to antiplatelet agents	Technically complex; requires expert interpretation. Not a POCT	Reference method. Uses different agonists activating various pathways
Multiplate analyzer®	Aggregation based on impedance	Can be used as POCT. Uses whole blood. Automated. Can detect antiplatelet effect	Inconsistent correlation with LTA. Uses anticoagulated blood under low shear conditions, unlike physiological conditions. Highly dependent on platelet count	Low platelet reactivity: < 19-30 U
Plateletworks®	Aggregation (difference in count before and after activation with agonists). Citrated whole blood	Small sample. Detects antiplatelet effect. Useful for monitoring	Requires calibration and manual processing. Only for antiplatelet monitoring. Interference in pseudothrombocytopenia, large platelets, and cell fragments	Scale ranges from 100% aggregation to 0% inhibition. Low platelet reactivity: < 80%
PFA®-100/200	Evaluates adhesion and aggregation (closure time, high shear condition). Citrated whole blood	POCT potential. Detects platelet dysfunction and von Willebrand disease. Sensitive to antiplatelet agents. Assesses bleeding risk	Results affected if platelet count < 50,000 or hematocrit < 25%	
VerifyNow®	Aggregation by optical turbidimetry	POCT, uses whole blood without processing. Detects antiplatelet effect. Automated with specific cartridges (AA, ADP/PG E1, TRAP)	Only evaluates effects of antiplatelet drugs. Sensitive to thrombocytopenia, lipidemia, anemia, and fibrinogen levels	Low platelet reactivity: < 85 PRU
TEG® (Platelet Mapping® module)	Global coagulation test. Evaluates activation and aggregation by MA and MA AA/ADP difference. Citrated whole blood	POCT with rapid results. Detects antiplatelet drugs	Identifies specific platelet function disorders	Low platelet reactivity defined as < 31 mm TEG MAADP or > 50–60% drop in MAADP vs TEG-MA kaolin
ROTEM® (ROTEM Platelet module)	Global coagulation test. Evaluates activation and aggregation via impedance aggregometry. Citrated whole blood	POCT with rapid results. Detects antiplatelet effect with 3 tests: ADPTM, ARATEM, TRAPTEM	Does not identify specific platelet function disorders	Limited device availability
Quantha®	Sonic estimation of elasticity by resonance (SEER sonorheometry)	Directly reports platelet contribution using PCS value, which is given in shear modulus units	Correlations and cut-offs in patients on antiplatelet agents are yet to be defined	Treatment threshold PCS < 75%

LTA: light transmission aggregometry; PCS: platelet contribution to clot stiffness; POCT: Point-of-Care test.

The analysis should ideally be performed between 30 minutes after collection and before 3-4 hours have passed, and it should be kept at room temperature.

Use of VETs

VETs use whole blood samples and provide information on the kinetics of clot formation from its initiation,

the generation of the platelet clot, its stabilization, and lysis. Therefore, unlike aggregation and cytometry methods that evaluate platelet function indirectly or via surface proteins, VETs assess the contribution of platelets and coagulation factors to this global clot formation by evaluating clot firmness or amplitude. In VETs, clot firmness is measured after platelet activation by thrombin and its polymerization with fibrin; thus, the

impact of platelet count on elasticity is very high.¹² These tests incorporate methods for inhibiting platelet function to eliminate the contribution of platelets to clot formation, thereby aiming to interpret their degree of function. In general, platelet contribution represents 80% of the clot firmness obtained in these tests.³⁴

Another relevant aspect is the relationship of platelet adhesion to hematocrit, making it a factor to consider in the results when evaluating platelet functionality.³⁵

The differing terminology among devices also causes confusion. For example, the maximum clot firmness (stiffness), which serves as a reference, is expressed in various ways: as MCF in ROTEM, MA in TEG, and CS (clot stiffness) in Quantra®. The latter also indicates values in terms of shear modulus (hPa), unlike the first two. From these MCF, MA, or CS values, platelet contribution could be established by eliminating fibrinogen's contribution to clot formation. However, using the difference between total clot amplitude and clot amplitude with only fibrinogen contribution would introduce a bias that underestimates the true platelet contribution. To avoid this bias, platelet contribution should be estimated by comparing amplitudes using shear modulus differences. The shear modulus (or elasticity) is not linearly associated with clot amplitude and would be better defined by this equation:

$$\text{Shear modulus (G, dyn/cm}^2\text{)} = (5,000 \times \text{amplitude [mm]}) / (100 - \text{amplitude [mm]})$$

This formula represents an exponential curve in the relationship, meaning that the greater the clot amplitude, the greater the difference between both measurements. For this reason, in bleeding patients with low amplitudes, platelet contribution has significant clinical relevance.³⁶

Thus, for ROTEM and TEG, this estimation of platelet contribution cannot be performed directly from the obtained stiffness values; it requires conversion to G, whereas Quantra® already expresses it in this unit.

It has also been shown that a linear relationship exists between changes in platelet counts and the maximum firmness results of VETs for platelet ranges between 28,000 and 91,000; however, outside this range, the changes are not dependent.

Regarding platelet inhibition, an association is only found with inhibition degrees between 68% and 82%, with VETs being insensitive to different inhibition degrees. Therefore, the viscoelastic method is considered to precisely evaluate antiplatelet-mediated inhibition and requires the development of tests with specific reagents. Another limitation is its performance under low shear conditions, which prevents the

identification of specific platelet dysfunctions. Thus, manufacturers of POCT VETs have developed different strategies to identify platelet functionality.

TEG® PLATELET MAPPING® ASSAY (TEG® 6S)

The TEG system incorporates a module, the PlateletMapping®, which automatically monitors platelet aggregation specifically alongside the VET. After heparinizing the sample to prevent clot formation, it allows antiplatelet monitoring through selective activation of the P2Y₁₂ receptor with ADP or the thromboxane pathway with AA. This enables measurement of the response to antiplatelet agents acting on these pathways. In the case of glycoprotein IIb/IIIa inhibitors, both the ADP test and the AA test are affected. This method has been validated against light transmission aggregometry as a reference method. First, maximum hemostatic activity is determined with a kaolin test, and then reptilase, factor XIIIa, and AA or ADP are added to a whole blood sample. Inhibition of platelet activation is calculated by comparing the kaolin test result as a reference; that is, the platelet contribution to global clot formation is obtained by comparing results with those obtained with TEG, but primarily aimed at identifying effects of inhibition by antiplatelet agents.

In settings such as trauma patients or cardiovascular surgery, it allows identification of patients with the effect of previous antiplatelet agents, although it has not been shown to have predictive value on mortality by itself.³⁷ It has shown predictive capacity for thrombotic and hemorrhagic risk in both cardiac and non-cardiac surgery patients.^{38,39}

In patients on dual antiplatelet therapy preoperatively, platelet function testing has been used to determine the surgical scheduling date. Thus, using MA_{ADP} reduces surgical delay time by 50% vs traditional suspension regimens.⁴⁰ Other described uses in cardiovascular surgery patients include association with VETs to improve the predictive capacity for perioperative bleeding, prediction of transfusion requirements, and guidance for antiplatelet therapy in patients with left ventricular assist devices.⁴¹

Overall, a cutoff point for proceeding or not with surgical intervention in antiplatelet patients is considered to be a 35% inhibition of ADP-induced aggregation.³⁹ Low platelet reactivity is defined by values < 31 mm TEG MA_{ADP} and in special circumstances, such as patients with circulatory assistance, values < 40 mm TEG MA_(activator).⁴² Various studies have suggested the utility of using TEG PlateletMapping® preoperatively

in antiplatelet patients to determine the moment of intervention and reduce hospital stay and costs.⁴³

As with other platelet function tests, other uses have also been described, such as monitoring the response to antiplatelet agents to individualize the type and dose of antiplatelet agents in patients who require it due to cardiac and cerebral vascular disease.

ROTEM® PLATELET ASSAYS

The platelet module is an add-on to the ROTEM machine that facilitates the analysis of platelet aggregation using an impedance aggregometry method.⁴⁴ It complements ROTEM's clot formation assessment, which does not detect the presence of platelet inhibitors.⁴⁵ It uses agonists ADP and AA in the tests respectively named ADPTEM and ARATEM; furthermore, it has a test that uses thrombin receptor activating peptide called TRAPTEM.

Studies have shown that the sample should rest for 15 minutes before analysis, and when a citrated sample is used, it should be evaluated within the following 60 to 120 minutes.⁴⁶ Reference intervals have been described for the impedance aggregometry method using other devices⁴⁷, and more recently, studies have been conducted to validate these intervals on the ROTEM® Platelet equipment.^{46,48}

Of note, the common use of citrated samples for study can cause artifacts in the *in vitro* detection of secondary platelet aggregation due to calcium depletion.⁴⁹ The use of tubes with hirudin instead of citrate can overcome this drawback. Nevertheless, some studies have established reference intervals for ADPTEM, ARATEM, and TRAPTEM, considering whether citrated or hirudin tubes are used.⁴⁶

Clinically, it has demonstrated utility in evaluating bleeding and transfusion risk in certain surgical settings.^{50,51}

QUANTRA® SYSTEM

This system is based on the sonorheometry method, using an ultrasound system to estimate elasticity by resonance (SEER) and thus evaluate the viscoelastic properties of whole blood. This system can provide more specific information than other VETs regarding platelet contribution to clot strength.⁵² However, studies establishing correlation with platelet function in patients with P2Y12 receptor inhibitors and determining cutoff points are necessary, as the PCS parameter actually represents a combination of platelet count and function.

The advantage of Quantra® PCS is that it directly shows platelet contribution via shear modulus difference, without needing to convert obtained values to shear modulus to infer the true platelet contribution, as occurs with other VETs. In general, a PCS value < 75% is considered a cutoff point for treatment, taking into account the clinical situation.

The PCS directly informs about platelet contribution to clot formation during the study. An independent association has been demonstrated between the values of PCS and platelet count and ADP-mediated platelet function.⁵² In clinical studies, this parameter has shown predictive capacity for the need for platelet transfusion in major surgery.⁵³

Conclusion

Evaluating platelet functionality represents a challenge due to the difficulty in recreating physiological *in vitro* conditions and the complex interaction of platelets with different receptors and mediators. Furthermore, there are significant differences in comparisons between various tests due to differences in methods and agonists used. All of this means that standardization guidelines have not been established, and there is significant variability in use and indications.

Economic impact of VETs use: savings in blood components and length of stay

The use of VETs should not be seen as an isolated intervention in the management of bleeding patients; rather, it should be framed within a much broader and more current context: patient blood management (PBM).

The World Health Organization (WHO) published a concise yet forceful document in 2021 on the urgency of implementing PBM programs after experiencing situations of tremendous scarcity of blood resources during the COVID-19 pandemic, which led to drastic reductions in donation volumes.

PBM is often identified with the correction of anemia and optimization of hemoglobin levels through iron and hematinic administration (PBM pillar 1). However, anemia can also be associated with medical and surgical processes and is linked to increased morbidity and mortality, prolonged length of hospital or ICU stays, and reduced quality of life.⁵⁴

VETs play a role precisely in those bleeding situations associated with surgical trauma, childbirth, or coagulopathies; they enable addressing the second

pillar of PBM, focused on minimizing blood loss and correcting coagulation. The results of the blood management program in Western Australia between 2008 and 2014 showed a 15% reduction in hospital stay and an economic saving of 18.5 million dollars in blood products.

Managing bleeding and efficiently and promptly correcting coagulation disorders are important, first and foremost for patient safety reasons, but also concerning the saving of health care costs and the sustainability of health care systems.

It is relevant to note the official prices (average prices) of blood components, VETs, and standard laboratory tests to determine the scope of savings with the use of VETs.

The rates published in the official gazettes of different autonomous communities are quite similar for the final price of blood components ready for transfusion, being €600 per platelet concentrate, €300 per red blood cell concentrate, and approximately €60 per unit of fresh plasma. Performing a global hemostasis VET with a cartridge system (ROTEM® Sigma, TEG6®, Quantra®) has an average cost of €100, while if ROTEM® Delta is used, each isolated determination costs about €25. Determining platelet function with cartridges on TEG® 6S costs €120. On the ROTEM® Deltadevice, each platelet receptor studied (AA, ADP, thrombin) costs €16.

Standard coagulation tests are cheaper than VETs (although the price varies in each hospital), but they do not provide immediate or rapid results and delay decision-making.

Transfusion of blood components is, *per se*, an incremental factor of morbidity, mortality, and length of stay,⁵⁵ with a proportional relationship between transfused volume and complications.⁵⁶ The saving of blood components already justifies the use of VETs *per se*, but there is also a reduction in care costs by reducing hospital stay. Unfortunately, it is difficult to establish exact calculations of these savings, although it can serve as a guide that the daily net cost of a patient in a critical care bed in our country varies between €800 and €1,500 (depending on the autonomous community), without accounting for personnel costs or administered drug.

The best-studied clinical scenario in the field of VETs is cardiac surgery, and numerous publications have demonstrated a reduction in transfusion volume and reoperation rates due to bleeding. The issue of savings in coagulopathy management in cardiac surgery was already addressed years ago by Spalding⁵⁷ (in 2007), with reductions of 25% in red blood cell consumption,

50% in platelet consumption, 80% in prothrombin complex concentrate and factor XIII, with cessation of recombinant activated factor VII use and, in contrast, doubling fibrinogen use. Spalding calculated a monthly cost reduction in blood products of €21,000, with an average cost of ROTEM® reagents and consumables of €1,580, and a reduction in the rate of re-sternotomies due to bleeding from 6.6% to 5.5%.

Of note, these benefits are enhanced if the use of VETs is associated with a transfusion strategy guided by algorithms. Karkouti et al.,⁵⁸ in 2016, demonstrated very significant reductions in bleeding rates, red blood cell and platelet transfusions, and a 26% decrease in reoperations at a time that coincided with increased complexity of the surgical cases.

The IMOTEC study,⁵⁹ whose results are pending publication, aims to evaluate the cost-effectiveness of using an algorithm-based VET and its impact on quality of life one year after surgical intervention, with special emphasis on the calculation of hospital costs per patient.

Whiting et al.⁶⁰ in their cost-effectiveness analysis of VET use in various scenarios, concluded that in cardiac surgery, the consumption of red blood cells, platelets, and plasma was reduced with the use of these tests, and they quantified a saving per patient of £43 with ROTEM®, £79 with TEG®, and £132 with Sonoclot®. In polytrauma patients, the calculated savings were greater: £688 with ROTEM®, £721 with TEG®, and £818 with Sonoclot®.

González et al.⁶¹ published interesting reductions in 28-day mortality with the use of VETs to guide transfusion therapy in polytrauma patients vs standard laboratory guidance.

A systematic review and meta-analysis by Soares⁶² in 2020 directly linked the use of VETs with a significant reduction in mortality, development of acute kidney injury, volume of administered red blood cells, and risk of platelet and plasma transfusion in surgical scenarios in general.

It is not easy, but it is common sense, to extrapolate that there is considerable savings if we avoid a patient entering renal replacement therapy through appropriate use of hemostatic and transfusional resources.

A 2014 review⁶³ extensively described many economic aspects of healthcare, which involves direct costs derived or not derived from healthcare (e.g., blood products and drugs are direct costs derived from healthcare, while transportation, social services, or legal fees are not derived from health care but do incur direct costs) and also indirect costs (productive losses due to

absenteeism or disability or morbidity and mortality). Clearly, the calculation is much more complex than it might seem *a priori*.

Clinical scenarios such as liver transplantation show contradictory evidence in the scientific literature regarding the usefulness of VETs, although their use is widespread, and they constitute a fundamental theragnostic tool in complex cases tending towards both hemorrhage and thrombosis. Randomized clinical trials by Bonnet⁶⁴ and Zamper⁶⁵ demonstrate a reduction in red blood cell and plasma transfusion with the use of thromboelastometry, although neither reaches conclusions of advantage regarding mortality, reoperation rates, or hospital stay.

Finally, in postpartum hemorrhage,⁶⁶ a reduction in plasma consumption and a slight tendency towards less bleeding have been demonstrated with the use of ROTEM to guide hemostasis.

Many other situations in clinical practice can benefit from the use of VETs and platelet function mapping, such as interventional radiology procedures involving vascular stent placement or large burn units, which undergo numerous fasciotomy and debridement interventions with a significant tendency to bleed. The evidence in these cases is very scarce.

In conclusion, the use of VETs is cost-efficient not only from the perspective of economic savings in blood components, which are expensive and scarce, but especially from the perspective of patient safety and optimizing their clinical outcome. The strict calculation of expense is, however, complex and multifactorial.

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Conflicts of interest

None declared.

Ethical considerations

Protection of persons and animals. The authors declare that no experiments on human beings or animals were conducted for this investigation.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data and does not require ethical approval. SAGER guidelines do not apply.

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