Coagulation Monitoring: Current Techniques and Clinical Use of Viscoelastic Point-of-Care Coagulation Devices

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Perioperative monitoring of blood coagulation is critical to better understand causes of hemorrhage, to guide hemostatic therapies, and to predict the risk of bleeding during the consecutive anesthetic or surgical procedures. Point-of-care (POC) coagulation monitoring devices assessing the viscoelastic properties of whole blood, i.e., thrombelastography, rotation thrombelastometry, and Sonoclot® analysis, may overcome several limitations of routine coagulation tests in the perioperative setting. The advantage of these techniques is that they have the potential to measure the clotting process, starting with fibrin formation and continue through to clot retraction and fibrinolysis at the bedside, with minimal delays. Furthermore, the coagulation status of patients is assessed in whole blood, allowing the plasmatic coagulation system to interact with platelets and red cells, and thereby providing useful additional information on platelet function. Viscoelastic POC coagulation devices are increasingly being used in clinical practice, especially in the management of patients undergoing cardiac and liver surgery. Furthermore, they provide useful information in a large variety of clinical scenarios, e.g., massive hemorrhage, assessment of hypo- and hypercoagulable states, guiding pro- and anticoagulant therapies, and in diagnosing of a surgical bleeding. A surgical etiology of bleeding has to be considered when viscoelastic test results are normal. In summary, viscoelastic POC coagulation devices may help identify the cause of bleeding and guide pro- and anticoagulant therapies. To ensure optimal accuracy and performance, standardized procedures for blood sampling and handling, strict quality controls and trained personnel are required.
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Perioperative monitoring of coagulation is important to diagnose potential causes of hemorrhage, to guide hemostatic therapies, and to predict the risk of bleeding during the consecutive surgical procedures.[1] Most commonly, routine laboratory-based coagulation tests (e.g., prothrombin time/International Normalized Ratio, activated partial thromboplastin time, fibrinogen) and platelet numbers are being used to assess the patients' current coagulation status. However, the value of these tests has been questioned in the acute perioperative setting[2] because there are delays from blood sampling to obtaining results (45–60 min), coagulation tests are determined in plasma rather than whole blood, no information is available on platelet function (PF) and the assays are performed at a standard temperature of 37°C rather than the patient's temperature.

Point-of-care (POC) coagulation monitoring devices assessing the viscoelastic properties of whole blood, i.e., thrombelastography (TEG®), rotation thrombelastometry (ROTEM®), and Sonoclot® analysis may overcome several limitations of routine coagulation tests.[3,4] Blood is analyzed at the bedside and not necessarily in the central laboratory, allowing faster turnaround times. The coagulation status is assessed in whole blood, allowing *in vivo* coagulation system interactions with platelets and red blood cells to provide useful information on PF. Furthermore, the clot development can be visually displayed in real-time and the coagulation analysis can be done at the patient's temperature. However, a significant difference between *in vitro* and *in vivo* coagulation has to be considered: viscoelastic coagulation tests measure the coagulation status under static conditions (no flow) in a cuvette (not an endothelialized blood vessel). Therefore, results obtained from these *in vitro* tests must be carefully interpreted after considering the clinical conditions (e.g., overt bleeding in the surgical site).

The aim of this article is to review the basic principles of the current viscoelastic POC coagulation analyzers, to outline their clinical use, and to evaluate

Figure 1. Viscoelastic point-of-care coagulation devices. A, Thrombelastograph, TEG (Hemoscope Corp., Niles, IL). B, Rotation Thrombelastometry, ROTEM (Pentapharm GmbH, Munich, Germany). C, Sonoclot Analyzer (Sienco Inc., Arvada, CO).
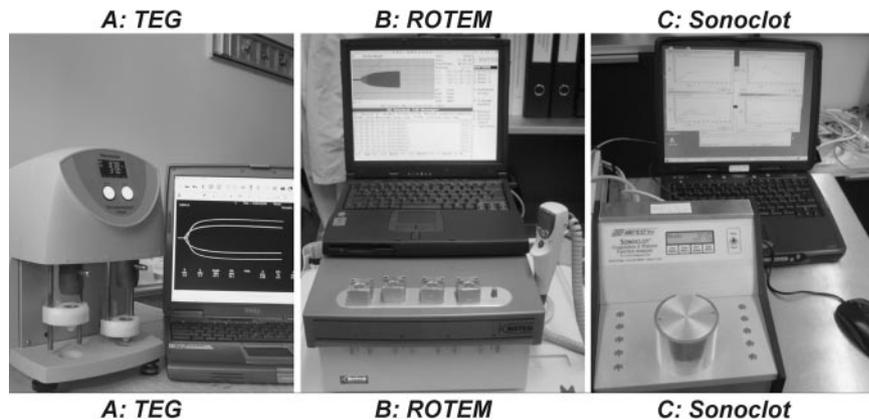
their ability to monitor different pharmacological substances interacting with hemostasis in the perioperative setting. Viscoelastic POC devices have also been used for coagulation testing of certain hemostatic disorders or syndromes in the hemostasis laboratory, but will not be discussed in this review.
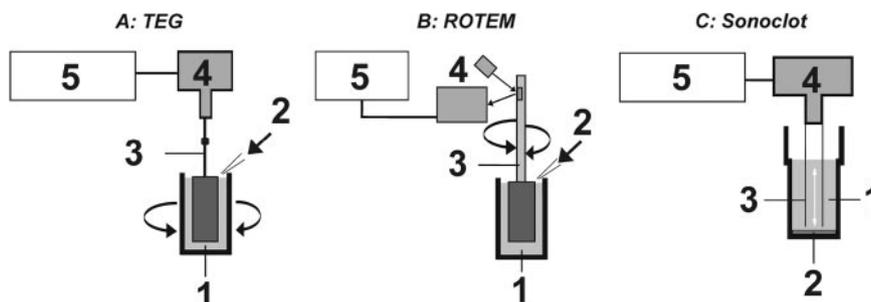
Thrombelastography, Thrombelastometry

Thrombelastography was first described by Hartert in 1948 as a method to assess the global hemostatic function from a single blood sample.[5] In the earlier literature, the terms "thrombelastography," "thrombelastograph," and "TEG®" have been used generically. However, in 1996 thrombelastograph® and TEG® became registered trademarks of the Hemoscope Corporation (Niles, IL) and from that time on these terms have been used to describe the assay performed using Hemoscope instrumentation only. Alternatively, Pentapharm GmbH (Munich, Germany) markets a modified instrumentation using the terminology rotation thrombelastometry, ROTEM®.[3]

The TEG/ROTEM® assess the viscoelastic properties of blood samples under low shear conditions. The TEG® (Fig. 1A) measures the clot's physical property by using a stationary cylindrical cup that holds the blood sample and oscillates through an angle of 4°45'. Each rotation cycle lasts 10 s. A pin is suspended in the blood by a torsion wire and is monitored for motion (Fig. 2A). The torque of the rotation cup is transmitted to the immersed pin only after fibrin-platelet bonding

has linked the cup and pin together. The strength of these fibrin-platelet bonds affects the magnitude of the pin motion. Thus, the output is directly related to the strength of the formed clot. As the clot retracts or lyses, these bonds are broken and the transfer of cup motion is again diminished. The rotation movement of the pin is converted by a mechanical-electrical transducer to an electrical signal, finally being displayed as the typical TEG® tracing (Fig. 3A). The ROTEM® instrument (Fig. 1B) uses a modified technology: the signal of the pin suspended in the blood sample is transmitted via an optical detector system, not a torsion wire, and the movement is initiated from the pin, not the cup (Fig. 2B).[6] Furthermore, the instrument is equipped with an electronic pipette.

TEG/ROTEM® both measure and graphically display the changes in viscoelasticity at all stages of the developing and resolving clot, i.e., the time until initial fibrin formation (TEG® reaction time; ROTEM® clotting time [CT]), the kinetics of fibrin formation and clot development (TEG® kinetics, α angle [α]; ROTEM® clot formation time, α angle [α]), the ultimate strength and stability of the fibrin clot (TEG® maximum amplitude [MA]; ROTEM® maximum clot firmness [MCF]), and clot lysis (fibrinolysis) (Table 2).[7,8] TEG/ROTEM® are fibrinolysis-sensitive assays and allow for diagnosis of hyperfibrinolysis in bleeding patients.[3,9] In our review, the variables from the TEG/ROTEM® will be referred to as they respectively relate to each instrument, for example, R/CT or MA/MCF.

Figure 2. Working principles of viscoelastic point-of-care coagulation devices. A, Thrombelastograph (TEG®): rotating cup with blood sample (1), coagulation activator (2), pin and torsion wire (3), electromechanical transducer (4), data processing (5). B, Rotation Thrombelastography (ROTEM®): Cuvette with blood (1), activator added by pipetting (2), pin and rotating axis (3), electromechanical signal detection via light source and mirror mounted on axis (4), data processing (5). C, Sonoclot: Blood sample in cuvette (1) containing activator (2), disposable plastic probe (3) oscillating in blood sample mounted on electromechanical transducer head (4), data processing (5).
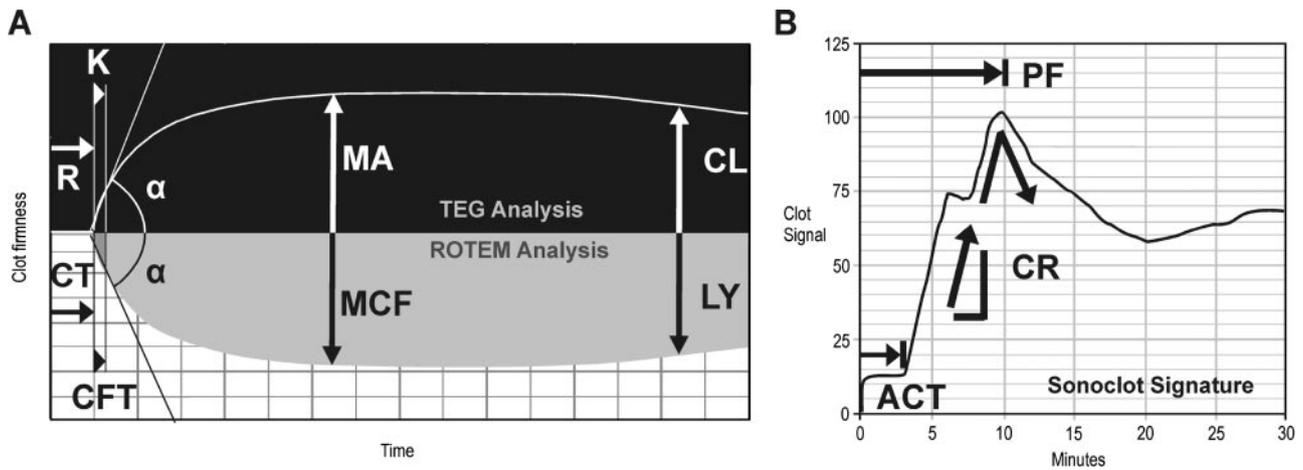
Figure 3. Typical tracings of viscoelastic point-of-care coagulation devices. A, upper side: Thrombelastograph (TEG®) tracing: r = reaction time; K = kinetics; α = slope between r and k; MA = maximum amplitude; CL = clot lysis. A, lower side: Rotation Thrombelastography (ROTEM®) tracing: CT = clotting time; CFT = clot formation time; α = slope of tangent at 2 mm amplitude; MCF = maximal clot firmness; LY = Lysis. B, Sonoclot Signature: ACT = activated clotting time; CR = clot rate; PF = platelet function. For detailed description and reference values, see Tables 2 and 3.

Commercially available tests for both technologies are listed in Table 1. Typically, blood samples are activated extrinsically (tissue factor) and/or intrinsically (contact activator). Furthermore, to determine fibrinogen levels, tests in the presence of a platelet inhibitor (e.g., cytochalasin D in fib-TEM) should be performed. This modified MA/MCF then represents the fibrin clot that developed in the absence of any platelets, i.e., the functional fibrinogen.[6,10] It has been shown that the MA/MCF of these modified tests correlates well with the fibrinogen assessed by the Clauss method (r = 0.85 [TEG 5000 User Manual] and r = 0.75[11]). The traditional Clauss method, however, determines fibrinogen levels indirectly: Excess thrombin is added to diluted plasma, the time is measured until a clot develops and fibrinogen is calculated with the help of a calibration curve. Although the Clauss method is considered a standard assay, it has been shown that hemodilution with colloids may interfere with this assays, reporting falsely high levels of fibrinogen.[12]

Although TEG® and ROTEM® tracings look similar (Fig. 3), the nomenclature and reference ranges are different (Table 2).[13] The differences may be explained by different cups and pins used in both systems (ROTEM® cups and pins are composed of a plastic with greater surface charge resulting in greater contact activation compared with cups and pins used in TEG®) and different proprietary formulas of the coagulation activators (composition, concentrations).[13] For example, if the same blood specimen is analyzed by TEG® and ROTEM® with their proprietary intrinsic coagulation activator, i.e., kaolin and in-TEM (partial thromboplastin phospholipids), respectively, the results obtained with both systems are significantly different: A recent study by Nielsen showed that the CT was nearly three-fold shorter than the R time and that the α-angle was 7% greater in the ROTEM® compared to the TEG®. It is therefore

critical that care be taken when practicing with TEG® and ROTEM® systems, especially if the clinician uses a treatment algorithm created with one system (e.g., TEG®) while analyzing patient samples with the other system (e.g., ROTEM®).[13] The repeatability of measurements by both devices is acceptable (summarized in Table 3) provided they are performed exactly as outlined in the users manuals [TEG 5000 User Manual].[6]

Sonoclot Analysis

The Sonoclot Analyzer (Fig. 1C, Sonoclot Coagulation & Platelet Function Analyzer, Sienco Inc., Arvada, CO) was introduced in 1975 by von Kaulla et al.[14] The principle of the Sonoclot analysis has been described in detail.[4] Briefly, the Sonoclot measurements are based on the detection of viscoelastic changes of a whole blood or plasma sample. To start a measurement, a hollow, open-ended disposable plastic probe is mounted on the transducer head. Then, the test sample is added to the cuvette containing different coagulation activators/inhibitors. After an automated mixing procedure, the probe is immersed into the sample and oscillates vertically in the sample. The changes in impedance to movement imposed by the developing clot are measured (Fig. 2C). Different cuvettes with different coagulation activators/inhibitors are commercially available (Table 1). Normal values for the Sonoclot Analyzer are shown in Table 4.

The Sonoclot Analyzer provides information on the entire hemostasis process both in a qualitative graph, known as the Sonoclot Signature (Fig. 3C) and as quantitative results: the activated clotting time (ACT), the clot rate (CR), and the PF. The ACT is the time from the activation of the sample until the beginning of a fibrin formation. This onset of clot formation is defined as an upward deflection

Table 1. Commercially Available Tests for Viscoelastic Point-of-Care Coagulation Devices

Assay	Activator inhibitor	Proposed indication
Thrombelastograph Hemostasis System (TEG®)		
Kaolin	Kaolin	Overall coagulation assessment and platelet function
Heparinase	Kaolin + Heparinase	Specific detection of heparin (modified Kaolin test adding heparinase to inactivate present heparin)
Platelet Mapping	ADP Arachidonic acid	Platelet function, monitoring antiplatelet therapy (aspirin, ADP-, GPIIb/IIIa inhibitors)
Native	None	Nonactivated assay. Also used to run custom hemostasis tests
Rotation Thrombelastometry (ROTEM®)		
ex-TEM	TF	Extrinsic pathway; fast assessment of clot formation and fibrinolysis
in-TEM	Contact activator	Intrinsic pathway; assessment of clot formation and fibrin polymerization
fib-TEM	TF + platelet antagonist	Qualitative assessment of fibrinogen levels
ap-TEM	TF + Aprotinin	Fibrinolytic pathway; fast detection of fibrinolysis when used together with ex-TEM
Hep-TEM	Contact activator + Heparinase	Specific detection of heparin (modified in-TEM test adding heparinase to inactivate present heparin)
eca-TEM	Ecarin	Management of direct thrombin inhibitors (e.g., hirudin, argatroban)
tif-TEM*	1:1000 TF	Extrinsic pathway; monitoring recombinant activated factor VIIa
na-TEM	None	Nonactivated assay. Also used to run custom hemostasis tests
Sonoclot® Coagulation and Platelet Function Analyzer		
SonACT	Celite	Large-dose heparin management without aprotinin
kACT	Kaolin	Large-dose heparin management with/without aprotinin
aiACT	Celite + Clay	Large-dose heparin management with aprotinin (aprotinin-insensitive ACT)
gbACT+	Glass beads	Overall coagulation and platelet function assessment
H-gbACT+	Glass beads + Heparinase	Overall coagulation and platelet function assessment in presence of heparin; detection of heparin
microPT*	1:1000 TF	Extrinsic pathway; monitoring recombinant activated factor VIIa
Native	None	Nonactivated assay. Also used to run custom hemostasis tests

ACT = activated clotting time; TF = tissue factor; ADP = adenosine diphosphate; GPIIb/IIIa = glycoprotein IIb/IIIa receptor.

* For research use only (not yet on the market by 2007).

of the Sonoclot Signature. Sonoclot's ACT corresponds to the conventional ACT measurement, provided that cuvettes containing a high concentration of a typical activators (celite, kaolin) are being used.[15–18] How can we compare R/CT of TEG/ROTEM® to the ACT determined by Sonoclot? The rotation of the pin of the TEG/ROTEM® begins to be impaired after fibrin-platelet bonding has linked the cup and pin together. Thus, the output is directly related to the strength of the formed clot. The output of Sonoclot's oscillating plastic probe, however, is sensitive to viscosity and monitors viscosity changes that occur during initiation of coagulation and clot development. Therefore, the

ACT reflects initial fibrin formation, whereas R/CT reflects a more developed, and later, stage of initial clot formation. This theoretical claim is being supported by a recent study by Tanaka et al.[19]: Simultaneously, ACT and R values were determined in kaolin activated whole blood samples. R values of TEG® were 1.5 fold (native blood samples), 3.9 fold (heparinized samples) or 4.2 fold (bivalirudin treated samples) higher compared with ACT values determined by Sonoclot.

Besides providing information on the initiation phase of coagulation, the Sonoclot Analyzer also measures the kinetics of fibrin formation and clot

Table 2. Nomenclature and Reference Values of Thrombelastography (TEG®) and Thrombelastometry (ROTEM®)

	TEG®	ROTEM®
Clotting time (period to 2 mm amplitude)	R (reaction time)	CT (clotting time)
	N (WB) 4–8 min	N (Cit, in-TEM) 137–246 s
	N (Cit, kaolin) 3–8 min	N (Cit, ex-TEM) 42–74 s
Clot kinetics (period from 2 to 20 mm amplitude)	K (kinetics)	CFT (clot formation time)
	N (WB) 1–4 min	N (Cit, in-TEM) 40–100 s
	N (Cit, kaolin) 1–3 min	N (Cit, ex-TEM) 46–148 s
Clot strengthening (alpha angle)	α (slope between r and k)	α (slope of tangent at 2 mm amplitude)
	N (WB) 47°–74°	N (Cit, in-TEM) 71°–82°
	N (Cit, kaolin) 55°–78°	N (Cit, ex-TEM) 63°–81°
Amplitude (at set time)	A	A
Maximum strength	MA (maximum amplitude)	MCF (maximum clot firmness)
	N (WB) 55–73 mm	N (Cit, in-TEM) 52–72 mm
	N (Cit, kaolin) 51–69 mm	N (Cit, ex-TEM) 49–71 mm
		N (Cit, fib-TEM) 9–25 mm
Lysis (at fixed time)	CL30, CL60	LY30, LY60

TEG®: N = normal values for kaolin activated TEG® in native whole blood (WB) or citrated and recalcified blood samples (Cit) [Haemoscope Corp.]. ROTEM®: N = normal values for contact (partial thromboplastin phospholipids, in-TEM), tissue factor (ex-TEM) and tissue factor plus platelet inhibitor cytochalasin D (fib-TEM) activated citrated and recalcified blood samples.[6] Reference values depend on reference population, blood sampling technique, other preanalytical factors, and coagulation activator.

Table 3. Coefficient of Variation for Thrombelastography (TEG®) and Thrombelastometry (ROTEM®)

	Coefficient of variation	
	TEG® (kaolin activated)	ROTEM® (in-, ex-TEM)
Clotting time	R = 13%	CT = 3%–12%
Clot kinetics	K = 4%	CFT = 3%–12%
Clot strengthening	α = 3%	α = 1%–5%
Maximum strength	MA = 6%	MCF = 1%–5%

ACT = activated clotting time; TF = tissue factor; ADP = adenosine diposphate; GPIIb/IIIa = glycoprotein IIb/IIIa receptor. * For research use only (not yet on the market by 2007).

TEG®: values are given for kaolin activated blood samples [Haemoscope Corp.].

ROTEM®: values are given for contact (in TEM) and tissue factor (ex-TEM) activated blood samples (6). For abbreviations see Table 2.

development, expressed as CR (the maximum slope of the Sonoclot Signature during initial fibrin polymerization and clot development). Furthermore, the function of the platelets is being analyzed and reported as PF (derived from the timing and quality of the clot retraction). The nominal range of values for the PF goes from 0, representing no PF (no clot retraction and flat Sonoclot Signature after fibrin formation), to approximately 5, representing strong PF (clot retraction occurs sooner and is very strong, with clearly defined, sharp peaks in the Sonoclot Signature after fibrin formation) (see manufacturer's reference).[20]

The Sonoclot Analyzer has been criticized because its results were influenced by age, sex, and platelet count.[21] Additionally, studies showed poor reproducibility of some of the measured variables, especially CR and PF.[22,23] However, others found the Sonoclot Analyzer to be valuable and reliable in patients undergoing cardiac surgical procedures[24,25] and the Sonoclot Analyzer has even demonstrated a precision close to that of thrombelastography.[26] In more recent studies, test variability of ACT values determined by Sonoclot were comparable to other established ACT analyzers (8%–9% on average).[15–18] Furthermore, test variability for PF determined by gbACT+ and H-gbACT+ (heparinase glass-bead test) was 6%–10% in a recent study assessing PF after administration of the glycoprotein IIb/IIIa (GPIIb/IIIa) antagonist tirofiban with or without heparin.[20]

Cardiac Surgery and Postoperative Care

Coagulation management of patients undergoing cardiac surgery is complex because of a balance between anticoagulation for cardiopulmonary bypass (CPB) and hemostasis after CPB. Furthermore, an increasing number of patients have impaired platelet function at baseline due to administration of antiplatelet drugs. During CPB, optimal anticoagulation dictates that coagulation is antagonized and platelets are prevented from activation so that clots do not form. After surgery, coagulation abnormalities, platelet dysfunction, and fibrinolysis can occur, creating a situation whereby hemostatic integrity must be restored. The complex process of anticoagulation with heparin, antagonism with protamine, and postoperative hemostasis therapy can be guided by POC tests that assess hemostatic function in a timely and accurate manner.[1]

Although studies report that viscoelastic POC coagulation devices may predict excessive bleeding after CPB, findings are not consistent and evidence supporting its usefulness as a predictor of bleeding is minimal.[27–29] Normal viscoelastic test results in a bleeding patient is unlikely due to a significant coagulopathy (high negative predictive value).[30] Therefore, viscoelastic POC tests may be useful in early identification and targeted treatment of a surgical bleeding.

The institution of transfusion algorithms based on TEG/ROTEM® parameters has been demonstrated to reduce transfusion requirements in adults and children undergoing cardiac surgery.[31–35] Furthermore, it has been recently shown that implementation of

Table 4. Reference Values for Sonoclot® Tests

Sonoclot® Assay	SonACT	kACT	gbACT+	aiACT
Activated clotting time (ACT)	85–145 s	94–178 s	119–195 s	62–93 s
Clot rate (CR)	15–45 U/min	15–33 U/min	7–23 U/min	22–41 U/min
		Clot Signal		

Values are given for native whole blood [Sienco Inc.]. For specific details on assays, see Table 1.

ROTEM®-guided coagulation management is cost-effective.[33] To detect nonheparin related hemostatic problems in the presence of large amounts of heparin, tests with heparinase have been developed (Table 1) and one study showed that implementation of an algorithm based upon heparinase-modified TEG resulted in a significant reduction of transfusion blood products.[36]

POC coagulation analyzers measuring ACT are routinely being used in cardiac surgical patients to guide heparin-induced anticoagulation and its reversal.[37–40] Besides standard ACT machines, viscoelastic POC analyzers also provide ACT results with comparable accuracy and performance. The ACT provided by the Sonoclot Analyzer is being used to guide heparin therapy, and several tests with different characteristics are commercially available (Table 1).[15–17] More recently, a novel assay has also been developed to measure ACT by TEG.[41]

Hepatic Surgery and Postoperative Care

Patients undergoing hepatic surgery, and particularly orthotopic liver transplantation (OLT), may have large derangement in their coagulation, making POC coagulation monitoring highly desirable. Problems associated with the defective organ (decreased synthesis and clearance of clotting factors, platelet defects) lead to impaired hemostasis and hyperfibrinolysis. Furthermore, systemic complications, such as sepsis and disseminated intravascular coagulation, further complicate a preexisting coagulopathy. Finally, marked changes in hemostasis in OLT occur during the anhepatic phase and immediately after organ reperfusion, mainly a hyperfibrinolysis resulting from accumulation of tissue plasminogen activator due to inadequate hepatic clearance and a release of exogenous heparin and endogenous heparin-like substances.

One of the first clinical applications of TEG was in the hemostatic management of OLT.[42] Although the value of TEG/ROTEM® in management of patients undergoing OLT has been established in the literature,[11,43,44] only one third of all OLT programs in the United States routinely used viscoelastic coagulation devices according to a national survey in 2002.[45] In addition to the hemorrhagic risk associated with hepatic surgery and OLT, hypercoagulability and thrombotic complication have been described in the postoperative period and can be adequately assessed with TEG/ROTEM®.[46,47] Only a few studies are available on the use of the Sonoclot Analyzer in hepatic

surgery and OLT; however, this technique has also been found to be useful in the perioperative coagulation management of these patients.[48,49]

Hypercoagulability, Thrombosis, and Other Clinical Situations

Recognized risk factors for thrombosis are generally related to one or more elements of Virchow's triad (stasis, vessel injury, and hypercoagulability).[50] Major surgery has been shown to induce a hypercoagulable state in the postoperative period, and this hypercoagulability has been implicated in the pathogenesis of postoperative thrombotic complications, including deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and vascular graft thrombosis.[51,52]

Identifying hypercoagulability with conventional nonviscoelastic laboratory tests is difficult unless the fibrinogen concentration or platelet count is markedly increased. However, hypercoagulability is readily being diagnosed by viscoelastic POC coagulation analyzers and TEG/ROTEM® (there are only few data on the use of Sonoclot) have been increasingly used in the assessment of postoperative hypercoagulability for a variety of surgical procedures.[51,53–55] Hypercoagulability is being diagnosed if the R/CT time is short and the MA/MCF is increased (exceeding 65–70 mm).[7,51]

Viscoelastic techniques have been used to assess blood coagulation in multiple clinical situations besides the assessment of hypercoagulability and outside the cardiac and hepatic units, but experience is limited. For example, TEG® has been successfully applied to assess the coagulation status in trauma patients.[55,56] Finally, there is a long list of publications on the successful use of TEG/ROTEM® and Sonoclot in other clinical areas, summarized in several reviews.[3,4,57]

Monitoring Anticoagulation

ACT measurements to guide heparin therapy and the use of modified POC coagulation tests with heparinase to assess the coagulation status in the absence of the anticoagulatory effects of heparin have been described above. However, besides the monitoring of unfractionated heparin, studies have shown that treatment with low molecular weight heparin and heparinoids (e.g., danaparoid) can also be assessed with POC viscoelastic tests.[58] Both standard and heparinase-modified tests have to be performed to

increase the sensitivity of TEG/ROTEM® for the effects of low molecular weight heparin and heparinoids.

Direct thrombin inhibitors are increasingly being used for prevention and treatment of venous thromboembolic events, management of patients with acute coronary syndromes and percutaneous coronary interventions and anticoagulation in patients with heparin-induced thrombocytopenia.[59] POC viscoelastic techniques, especially the ecarin clotting time (ecarin directly activates thrombin), have proven helpful in assessing the hemostasis system in patients treated with direct thrombin inhibitors.[60,61]

Monitoring Antiplatelet Therapy/PF

In Western countries, antiplatelet therapy is increasingly being prescribed for primary and secondary prevention of cardiovascular disease to decrease the incidence of acute cerebro- and cardiovascular events. Antiplatelet drugs typically target to inhibit cyclooxygenase 1/thromboxaneA2 receptors (e.g., aspirin), adenosine diphosphate (ADP) receptors (e.g., clopidogrel) or GPIIb/IIIa receptors (e.g., abciximab, tirofiban). Although antiplatelet drugs are thought to work primarily by decreasing platelet aggregation, they also have been shown to function as anticoagulants: Activated platelets facilitate thrombin generation by providing a catalytic cell surface on which coagulation reactions may occur and they release activated Factor V. Vice versa, anticoagulants may also alter PF.[62,63] Because platelets play a key role in overall coagulation, the assessment of the PF (more than their number) is critical in the perioperative setting.[64,65]

Traditional assays, such as turbidimetric platelet aggregometry, are still considered a clinical standard for PF testing. However, conventional platelet aggregometry is labor-intensive, costly, time-consuming, and requires a high degree of experience and expertise to perform and interpret. Furthermore, platelets are tested under relatively low shear conditions in platelet rich plasma, conditions that do not accurately simulate primary hemostasis.[65]

Viscoelastic POC coagulation analyzers may provide information on PF but these tests also assess coagulation under low shear conditions. The MA/MCF from TEG/ROTEM® reflects overall PF and fibrinogen levels. It is recommended that two different tests be run simultaneously, e.g., ex-TEM (tissue factor activated test) and fib-TEM (ex-TEM plus cytochalasin D to inhibit PF): The difference between clot firmness of ex-TEM and fib-TEM then represents the platelet contribution. However, since conventional TEG/ROTEM® are not sensitive to targeted pharmacological inhibition, a more sophisticated test has recently been developed for the TEG to specifically determine PF in the presence of antiplatelet therapy (PlateletMapping™).[66,67] Briefly, the maximal hemostatic activity of the blood specimen is first measured by a kaolin activated whole blood sample. Then, further measurements are performed in the presence of heparin

to eliminate thrombin activity: Reptilase and Factor XIII (Activator F) generate a crosslinked fibrin clot to isolate the fibrin contribution to the clot strength. The contribution of the ADP or thromboxane A2 receptors to the clot formation is provided by the addition of the appropriate agonists, ADP or arachidonic acid. The results from these different tests are then compared with each other and the PF calculated.[68]

The Sonoclot Analyzer has also been shown to reliably detect pharmacological GPIIb/IIIa inhibition.[20,69] To obtain reliable results for PF, cuvettes containing glass beads for specific platelet activation (gbACT+) should be used.[20]

Monitoring Procoagulant Therapy

The modern practice of coagulation management is based on the concept of specific component therapy and requires rapid diagnosis and monitoring of the pro-coagulant therapy. It has been shown, for example, that platelet transfusion in the perioperative period of coronary artery bypass graft surgery is associated with increased risk for serious adverse events.[70] Clinical judgment alone, or combined with conventional nonviscoelastic laboratory tests, cannot predict who will benefit from a platelet transfusion in the acute perioperative setting. Therefore, the most recent guidelines on perioperative blood transfusion and blood conservation of The Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists clearly state that transfusion of coagulation products should be preferably guided by POC tests that assess hemostatic function in a timely and accurate manner.[1]

Fibrinogen is a key coagulation factor (substrate to form a clot) and isolated fibrinogen substitution in severe models of dilutional coagulopathy has been shown to improve clot strength and reduce blood loss.[71] Supplementary administration of prothrombin complex (concentrate of factor II, VII, IX, X, antithrombin III, protein C) additionally improved initiation of coagulation and reversed the dilutional coagulopathy.[72] As mentioned earlier in this review, fibrinogen levels can be assessed by measuring clot strength (MCF/MA) in the presence of platelet inhibition (e.g., fib-TEM)[11] or by assessing Sonoclot's CR.[73]

Recombinant activated factor VII (rVIIa) treatment is currently approved for patients with congenital or acquired hemophilia with antibodies to factor VIII or IX (United States and Europe), factor VII deficiency, and Glanzmanns thrombasthenia (Europe). However, rVIIa is increasingly used in off-label indications to control severe bleeding (e.g., major trauma, surgical interventions, intracerebral hemorrhage) in theory, by locally activating hemostasis at sites of vascular injury. The resulting thrombin burst then leads to the formation of a fibrin clot, provided that fibrinogen levels are sufficient. Consensus guidelines have been published for these off-label indications, but it is still unclear how to reliably monitor patients receiving rVIIa.[74,75] To better

study the result of thrombin generation (i.e., fibrin polymerization, factor XIII activation, factor XIIIa crosslinking of fibrin polymers, and platelet activation), modified TEG/ROTEM® parameters based on the first derivative of original TEG/ROTEM® tracing have been introduced recently: maximum velocity of clot formation (maximum rate of thrombus generation, MaxVel), time to reach MaxVel (time to maximum thrombus generation, tMaxVel) and total thrombus generation (area under the curve).[76–78] These parameters are supposed to be more sensitive to rVIIa than standard TEG/ROTEM® parameters, and dilute tissue factor should be used as coagulation activator for best sensitivity.[57] In a preliminary study, we were able to monitor the effects of rVIIa *in vitro* after severe hemodilution using the new diluted tissue factor activated tests from ROTEM (tif-TEM) and Sonoclot (microPT).[73,79]

Factor XIII is needed for cross-linking fibrin, thereby stabilizing the clot, increasing clot strength, and resistance to fibrinolysis. There are case reports on patients with unexplained intraoperative bleeding due to decreased factor XIII and subsequent stabilization after substitution. Impaired clot strength and increased lysis have been observed.[80]

Antifibrinolytic drugs (aprotinin, tranexamic, and ϵ aminocaproic acid) are used mostly in cardiac surgery to reduce bleeding and transfusion requirements. Aprotinin may interact with POC coagulation assays, prolonging for example celite activated ACT tests. Therefore, kaolin or aprotinin-insensitive ACT should be used to guide heparin therapy in these patients.[16,17] Antifibrinolytic therapy may be predicted *in vitro* in TEG/ROTEM with certain tests already containing an antifibrinolytic drug (e.g., ap-TEM). Ap-TEM predictive for a good patient response would then show a significantly improved initiation/propagation phase compared with ex-TEM and or disappearance of signs of hyperfibrinolysis. There are no conclusive studies on monitoring desmopressin therapy.

Critiques of POC Coagulation Monitoring

Several concerns have been raised using viscoelastic POC coagulation tests because these tests are hard to standardize. The blood collection site, processing of the sample (native vs citrated samples, time delay between collection and measurement—-for citrated samples a minimum rest time of 30 min is required), patient age, and gender may significantly affect the results of these tests.[3] Furthermore, equipment, activators and other modifications will alter the assay specificity. All these factors have to be considered when interpreting results in the literature and have to be known and standardized when running tests in a single center.

As with all POC devices, there is a concern that the devices are not adequately maintained, supervised, and that quality controls are not done on a regular basis. Furthermore, nonlaboratory personnel are running these POC tests, which may lead to further errors if they are not adequately trained (TEG and Sonoclot have been listed as moderate complexity tests by the Clinical Laboratory Improvement Amendment). Alternatively, to minimize these problems and release the operating room/intensive care unit personnel, the so-called POC coagulation analyzers have been recently moved into the central laboratory in some hospitals, thereby no longer being located at the bedside. A trained person runs the viscoelastic coagulation test and the results (evolving signatures) are submitted real-time to the patient's site.

CONCLUSIONS

Viscoelastic POC coagulation analyzers are being used in certain clinical situations known for their inherent risk of coagulation disorders, especially in the management of patients undergoing cardiac and liver surgery. Furthermore, they provide useful information in a large variety of clinical scenarios, e.g., massive hemorrhage, assessment of hypo- and hypercoagulable states and monitoring of pharmacological treatment with anti- and procoagulant drugs. The advantage of these techniques is that they have the potential to measure the entire clotting process, starting with fibrin formation and continue through to clot retraction and lysis at the bedside, with minimal time delays. Although physiological clot development is better depicted as a result of whole blood analysis of the coagulation status, these techniques measure hemostasis under static conditions *in vitro*, and the results of these tests must be carefully interpreted correlating them to clinical conditions. Finally, to bring viscoelastic POC coagulation analyzers to the next level in the future, several improvements, such as easier handling of blood samples, full automation, simultaneous testing with multiple activators, integrated analyzing software, and high robustness of the devices, would be highly desirable.

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