Viscoelastic Coagulation Testing: Use and Current Limitations in Perioperative Decision-making

Gabor Erdoes, M.D., Ph.D., Andreas Koster, M.D., Ph.D., Jerrold H. Levy, M.D., F.C.C.M.

Rapid diagnosis and therapy of coagulopathy plays a key role in the care of the severely bleeding patient in major trauma, postpartum hemorrhage, or major surgery. Perioperative diagnostic and treatment algorithms are mostly guided by viscoelastic point-of-care coagulation assays. There is convincing evidence that implementing transfusion algorithms based on the results of viscoelastic point-of-care coagulation tests can reduce transfusions and lead to improved patient outcomes (table 1).[1–4] In the perioperative period, two assays are most often used: the kaolin thromboelastography (TEG) and the functional fibrinogen TEG as part of TEG-based viscoelastic monitoring and the tissue factor–activated rotational thromboelastometry (ROTEM, also called "EXTEM") and fibrinogen ROTEM (also called "FibTEM") assays as part of ROTEM-based viscoelastic monitoring. These assays are designed to help answer basic questions regarding treatment of perioperative coagulopathy, such as when should the clinician transfuse platelets, administer fibrinogen concentrate, or give plasmatic coagulation factors by transfusing fresh frozen plasma (FFP) or prothrombin complex concentrates (PCCs)? And when is the administration of an antifibrinolytic agent justified? However, is important to realize that the standard TEG/ROTEM assays are not sensitive and specific to adequately detect platelet inhibition,[5] effects of direct oral anticoagulants, or inherited bleeding disorders (e.g., hemophilia, von Willebrand disease).[6] Thus, the diagnosis of these rather specific conditions is better made preoperatively as part of a routine diagnostic workup.[7]

In this Clinical Focus Review, we aim to reevaluate the current literature published on viscoelastic point-of-care tests and their impact on clinical decision-making. In particular, we were interested in which fundamental questions affecting routine patient care in the perioperative period could be answered by TEG and ROTEM assays and which could not. Because this is not a systematic review, we did not consider specific methodologic criteria for study selection or analysis. Nevertheless, we agreed on the search criteria and the selection of relevant publications. In addition to randomized controlled trials, systematic reviews, meta-analyses, society recommendations, and guidelines were assessed and implemented if deemed relevant. The interpretations are intended to emphasize the clinical aspects of standard viscoelastic point-of-care assays and to highlight specific areas that warrant further development.

Viscoelastic Testing for Administration of Platelets and Fibrinogen Concentrate

A basic assumption of TEG and ROTEM is that the amplitude of the viscoelastic signal is a composite of the interaction of platelets and fibrinogen. In the functional fibrinogen TEG, abciximab, a glycoprotein IIb/IIIa receptor inhibitor, is used, whereas the fibrinogen ROTEM assay uses cytochalasin D, an inhibitor of actin polymerization in platelets.[8,9] The addition of the antiplatelet agent reduces the platelet-mediated clot activation signal to selectively evaluate the fibrinogen component of clot strength. In turn, platelet contribution is calculated by the difference between the viscoelastic amplitude of the tissue factor–activated ROTEM and fibrinogen ROTEM.[10]

However, two major considerations call into question the validity of the results obtained with the above-mentioned assays. First, there are convincing data showing that there is residual platelet noise in the fibrinogen assays caused by incomplete inhibition of platelet aggregation.[8,9] This is more pronounced when a platelet glycoprotein IIb/IIIa receptor inhibitor is used and less pronounced when cytochalasin D is used. The combination of the agents leads to complete inhibition of platelet aggregation and thereby prevents any residual "platelet noise."[8,9] Second, there is emerging evidence that it is not the amplitude of the viscoelastic signal but the clot elasticity ($100 \times$ viscoelastic amplitude [mm]/$100 -$ viscoelastic amplitude [mm]) that more accurately reflects the platelet contribution to clot. Early theoretical considerations in this regard[11] have recently been confirmed by studies of blood samples from patients who received platelet receptor $P2Y_{12}$ inhibitor therapy before cardiac surgery.[12] The same research group demonstrated that the correlation of the viscoelastic amplitude with platelet count and adenosine diphosphate–induced platelet aggregation was weak.[12] The difference in platelet-specific elasticity between the tissue factor–activated ROTEM and fibrinogen ROTEM,

Table 1. Viscoelastic Testing and Its Association with Transfusion Requirements in Different Settings

Reference	Study Type (No. of Patients)	Investigated Devices (vs. Control Group)	Clinical Setting (Number of Studies)	Main Results
Whiting et al.[1]	Systematic review and cost-effectiveness analysis (cardiac: 1,089; trauma: 4,217; postpartum hemorrhage: 245)	TEG, ROTEM, or Sonoclot (Sienco Inc., USA) (vs. no test or standard laboratory tests)	Cardiac setting: cardiac surgery (11 randomized controlled trials and 3 prediction studies) Noncardiac setting: trauma (1 randomized controlled trial and 15 prediction studies); postpartum hemorrhage (2 prediction studies)	Viscoelastic testing was associated with significant reduction in erythrocyte transfusion (relative risk, 0.88; 95% CI, 0.80 to 0.96; six studies), platelet transfusion (relative risk, 0.72; 95% CI, 0.58 to 0.89; six studies), and FFP transfusion (relative risk, 0.47; 95% CI, 0.35 to 0.65; five studies)
Conclusion: Viscoelastic testing is more effective than standard laboratory testing.				
Wikkelsø et al.[2]	Systematic review, meta-analysis and trial sequential analysis (1,185)	TEG or ROTEM (vs. clinical judgment/standard laboratory tests)	Bleeding patients: cardiac surgery (13 randomized controlled trials) liver transplantation (1 randomized controlled trial); burn wound excision (1 randomized controlled trial)	TEG/ROTEM-guided management reduced platelet transfusion [relative risk (95% CI) 0.73 (0.60 to 0.88); I2 = 0%, 10 studies, 832 participants], FFP transfusion [relative risk (95% CI) 0.57 (0.33 to 0.96); I2 = 86%, 10 trials, 832 participants] and erythrocyte transfusion [relative risk (95% CI) 0.86 (0.79 to 0.94); I2 = 0%, 10 trials, 832 participants] and overall mortality [3.9% vs. 7.4%, relative risk (95% CI) 0.52 (0.28 to 0.95); I2 = 0%, 8 trials, 717 participants]. No difference in portion of re-interventions [relative risk (95% CI) 0.75 (0.50 to 1.10); I2 = 0%, 9 trials, 887 participants].
Conclusion: TEG/ROTEM-guided therapy may reduce the need for blood products in patients with bleeding.				
Dias et al.[3]	Systematic review and meta-analysis (882)	TEG 5000 and 6S (vs. no TEG)	Perioperative setting: cardiac surgery (7 randomized control trials); liver surgery (2 randomized control trials)	TEG-guided management reduced platelet transfusion (P = 0.004), FFP transfusion (P < 0.001), erythrocyte transfusion (P = 0.14), operating room length of stay (P = 0.005), intensive care unit length of stay (P = 0.04), and bleeding rate (P = 0.002). Mortality remained comparable between the treatment and the control group.
			Emergency setting: trauma (1 randomized control trial)	TEG-guided management reduced platelet transfusion (P = 0.04) and FFP transfusion (P = 0.02) Mortality was lower in the TEG group (P = 0.049).
Conclusion: TEG-guided hemostatic therapy improves blood product management and patient outcome.				
Meco et al.[4]	Systematic review, meta-analysis, meta-regression, and trial sequential analysis (1,035)	TEG or ROTEM (vs. clinical judgment)	Perioperative setting: cardiac surgery (7 randomized control trials)	TEG/ROTEM-guided management reduced FFP transfusion (risk difference, 0.22; 95% CI, 0.11 to 0.33; P < 0.0001) and erythrocyte transfusion (odds ratio, 0.61; 95% CI, 0.37 to 0.99; P = 0.04) but not platelet transfusion (odds ratio, 0.61; 95% CI, 0.32 to 1.15; P = 0.12). TEG/ROTEM-guided management reduced postoperative bleeding at 12 h: −178.7 (95% CI, −308.9 to 48.4; P = 0.007); the need for redo surgery unrelated to surgical bleeding (odds ratio, 0.51; 95% CI, 0.28 to 0.94; P = 0.03) and postoperative intensive care unit stay (odds ratio, −4.03; 95% CI, −6.28 to −1.78; P = 0.005) but not mortality (odds ratio, 0.57; 95% CI, 0.18 to 1.74; P = 0.28).
Conclusion: TEG/ROTEM-guided hemostatic therapy is effective in reducing allogenic blood product exposure and postoperative bleeding after surgery and improves patient outcome.				

FFP, fresh frozen plasma; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

however, provided a strong correlation with platelet count and even a moderate correlation with an adenosine diphosphate–induced platelet aggregation assay.

Trigger for Platelet Transfusions in Clinical Recommendations

The United States–based Society of Cardiovascular Anesthesiologists has published a practical approach using both TEG and ROTEM for targeted blood component therapy.[13] Critical thresholds for platelet transfusion were defined for the viscoelastic amplitude after 10 min in ROTEM and the maximum amplitude in TEG (table 2).[9,13–17] The trigger for platelet transfusion, however, was not given as a defined value of these parameters but as a more open synoptic approach also considering a minimum target value for fibrinogen in the functional fibrinogen assays.

Table 2. Societies' Guidelines on Coagulation Factor Substitution and Antifibrinolytic Therapy[9,13-17]

Medical Area	Obstetrics (Postpartum Hemorrhage)	Trauma		Cardiac Surgery with Cardiopulmonary Bypass	
Society	British Society of Haematology	British Society of Haematology	European Trauma Guidelines	Society of Cardiovascular Anesthesiologists	European Association of Cardiothoracic Anaesthesiology
General statements		Normal TEG/ROTEM parameters enable the team to monitor closely without immediate activation of the major hemostatic resuscitation protocol	Early and repeated monitoring of hemostasis with traditional laboratory parameters and/or point-of-care viscoelastic methods	Individualized therapy with point-of-care guided algorithms recommended because they are associated with improved patient outcomes	
Platelet concentrates				Fibrinogen ROTEM viscoelastic amplitude at 10 min > 10 mm; tissue factor–activated ROTEM viscoelastic amplitude at 10 min < 40 mm TEG functional fibrinogen > 8 mm; maximum amplitude < 40 mm	
FFP, PCC				Tissue factor–activated ROTEM clotting time > 100 s Heparinase TEG reaction time > 12 min	
Fibrinogen concentrate cryoprecipitate	Fibrinogen ROTEM viscoelastic amplitude at 5 min < 7 mm Fibrinogen ROTEM viscoelastic amplitude at 5 min < 12 mm (in ongoing bleeding)		Major bleeding with functional fibrinogen deficit (plasma Clauss fibrinogen concentration <1.5 g/l) Fibrinogen ROTEM maximum clot firmness < 8 to 10 mm* Functional fibrinogen < 12 mm*	Fibrinogen ROTEM viscoelastic amplitude at 10 min < 10 mm; tissue factor–activated ROTEM viscoelastic amplitude at 10 min < 40 mm TEG maximum amplitude < 40 mm; functional fibrinogen < 8 mm	Fibrinogen ROTEM maximum clot firmness ≤4 to 6 mm recommended Fibrinogen ROTEM maximum clot firmness 6 to 8 mm considered Fibrinogen ROTEM maximum clot firmness > 9 mm targeted
No fibrinogen concentrate	Fibrinogen ROTEM > 12 mm				Fibrinogen ROTEM maximum clot firmness > 14 mm
Antifibrinolytic therapy	Tranexamic acid should not be withheld based on TEG/ROTEM results			Contact phase–activated ROTEM or tissue factor–activated ROTEM maximum lysis > 7% at 30 min or maximum lysis < 15% at 60 min TEG clot lysis at 30 min > 7.5%	

FFP, fresh frozen plasma; PPC, prothrombin complex concentrate; ROTEM, rotational thromboelastometry; TEG, thromboelastography.
*Added on the basis of the work of Ranucci *et al*.[9] and de Vries *et al*.[17]

Trigger for Fibrinogen Concentrate or Cryoprecipitate in Clinical Recommendations

Recommendations for the replacement of concentrated fibrinogen based on viscoelastic test results are available from the Pan-European multidisciplinary Task Force for Advanced Bleeding Care in Trauma (hereafter referred to as the European trauma guidelines),[14] the Society of Cardiovascular Anesthesiologists,[13] and the Haemostasis and Transfusion Subcommittee of the European Association of Cardiothoracic Anaesthesiology and Intensive Care (table 2).[15] In the European trauma guidelines, target values for fibrinogen plasma levels were only defined for the standard laboratory method. At the same time, viscoelastic tests were considered equivalent. The defined transfusion threshold for fibrinogen administration (less than 1.5 g/l plasma fibrinogen level) in the actively bleeding patient correlated well with a fibrinogen ROTEM maximal clot firmness of less than 10 mm in healthy people.[9]

In the recommendation from the Society of Cardiovascular Anesthesiologists, similarly, a synoptic approach was used.[13] In the European recommendations, trigger values for fibrinogen supplementation with fibrinogen concentrate, as well as fibrinogen plasma thresholds prohibiting administration of exogenous fibrinogen, have been defined. A similar approach was followed for postpartum hemorrhage by the British Society for Haematology (table 2).

Viscoelastic Testing for Repletion of Plasma Coagulation Factors

The clotting time in ROTEM and the reaction time (*r*) in kaolin TEG reflect the state of the plasmatic coagulation system by measuring the amount of time until the formation of a first fibrin network. The kaolin TEG activates whole blood *via* the intrinsic contact system, and in this respect is similar to the activated partial thromboplastin time, which is sensitive to deficiencies in the coagulation factors II, V, VIII, IX, and X and fibrinogen,[18] but not in factor VII.[19] In the tissue factor–activated ROTEM assay, tissue factor and the heparin reversal agent hexadimethrine bromide are added, which binds and neutralizes heparin up to a plasma concentration of 4 IU/ml. The tissue factor–activated ROTEM assay therefore shows similarities to the prothrombin time and the international normalized ratio (INR) and is sensitive to deficiencies in the extrinsic and common pathways represented by factors II, V, VII, and X and fibrinogen.[18]

In clinical reality, the decision to transfuse plasma coagulation factors is based on clot time or reaction time. Current four-factor PCCs contain the vitamin K–dependent coagulation factors II, VII, IX, and X. The concentrates were originally developed to reverse the effect of warfarin and other vitamin K antagonists. However, in trauma and cardiac surgery, these concentrates are increasingly used to treat major bleeding and coagulopathy as a "hemostatic resuscitation."[20] In the bleeding patient with preoperative warfarin use, the decision to administer PCC is usually based on the preoperative INR.[20] However, in the severely bleeding patient not taking warfarin, the decision to transfuse FFP and/or PCC should ideally be based on laboratory and viscoelastic test values (see below), which than should also be used to monitoring their effects after administration.

Unfortunately, the relevant data supporting PCC use are sparse despite their increasing administration. However, there is evidence suggesting that clotting time in tissue factor–activated ROTEM may be an appropriate tool to use. In ex-vivo studies using blood samples from patients on vitamin K antagonist therapy, the correlation between the clotting time in tissue factor–activated ROTEM and the reaction time in kaolin TEG with INR was investigated.[21,22] As a result, clotting time in tissue factor–activated ROTEM correlated with INR, whereas reaction time in kaolin TEG was insensitive. Clotting time in tissue factor–activated ROTEM (reference range, 38 to 79 s) for an INR value between 1.2 and 2.0 clustered around 80 s, for an INR value between 2 and 3 around 100 s, and for an INR of more than 3 around 140 s.

The fact that clotting time in tissue factor–activated ROTEM is sensitive to the loss of the vitamin K–dependent coagulation factors raises the question of whether targeted replacement of these factors by transfusion of PCC can also be monitored with tissue factor–activated ROTEM assay. In a retrospective study of trauma patients in whom coagulation factor concentrates were transfused based on ROTEM results, administration of (median) 1,200 IU PCC, which approximates 15 IU/kg PCC, normalized clotting time in tissue factor–activated ROTEM from (median) 101 to 77 s. In contrast, clotting time in a contact phase–activated ROTEM (comparable to kaolin TEG) remained unchanged.[23]

Trigger for FFP and/or PCC in Clinical Recommendations

In the Society of Cardiac Anesthesiology recommendations, transfusion of 10 to 15 ml/kg of FFP or a low dose of PCC (not defined) is recommended when clotting time in tissue factor–activated ROTEM or the reaction time in heparinase TEG is significantly prolonged (table 2).[13] Of note, the European recommendations for hemostatic resuscitation in trauma recommend a dose of 25 IU/kg of a PCC, whereas in cardiac surgery patients, an initial dose of 12.5 IU/kg (similar to that suggested by the U.S. recommendations) should be considered because of the inherent risk of thromboembolism.[20] In the European trauma guidelines, the authors point out the possible influence of hypofibrinogenemia on clotting time in tissue factor–activated ROTEM.[14] Therefore, PCC should be given only when fibrinogen levels are less than 1.5 g/l (corresponding to a fibrinogen ROTEM maximal clot firmness of less than 10 mm), and clotting time in tissue factor–activated ROTEM is prolonged or remains prolonged after replacement of fibrinogen.

Viscoelastic Testing of Fibrinolytic State

In the viscoelastic tests, clot lysis is determined after 30 or 60 min by calculating the decrease in maximal clot firmness on ROTEM or the maximal amplitude on TEG. The evaluation of the fibrinolytic system is complex because local and systemic fibrinolysis occurs in parallel and involves blood flow and cells, especially platelets.[24] In trauma patients, there is a distinction between hyperfibrinolysis, hypofibrinolysis, and "fibrinolytic shutdown," a severe condition in which even physiologic fibrinolysis is halted, and disseminated microembolism can occur, damaging multiple organs. This has implications for the patient's prognosis and presumably for therapy.[25,26] Study results are, however, conflicting again. In a large prospective cohort study in trauma patients, fibrinolysis was defined as a reduction of tissue factor–activated ROTEM maximal clot firmness of more than 15% measured 60 min after the onset of clot formation. Additionally, plasmin–antiplasmin complexes were measured.[27] The study showed that the tissue factor–activated ROTEM assay could detect hyperfibrinolysis in only 5% of patients when plasmin–antiplasmin complexes were elevated to 30 times normal. However,

in 57% of patients with hyperfibrinolysis detected by plasmin–antiplasmin complexes more than twice the normal level, 28-day mortality was significantly increased compared to patients without evidence of hyperfibrinolysis, as indicated by elevated plasmin–antiplasmin complexes (12% *vs.* 1%, $P < 0.001$). These results were recently confirmed in another prospective multicenter observational cohort study in 914 trauma patients.[28] In a large prospective two-center study involving 2,540 severely injured patients, the diagnosis of fibrinolysis was based on the rapid TEG assay, which contains both kaolin and tissue factor.[29] Hyperfibrinolysis was defined as a decrease in maximum amplitude by more than 3% within 30 min, physiologic fibrinolysis as a decrease between 0.8% and 3%, and fibrinolytic shutdown as a decrease in maximal amplitude of less than 0.8%. Patients with hyperfibrinolysis had the worst outcomes, with a mortality rate of 34%, followed by those with fibrinolytic shutdown (22%) and patients with physiologic fibrinolysis (14%; $P < 0.0001$). A recent analysis of 549 patients in the randomized controlled Pragmatic Optimized Ration Platelet and Plasma Trial provided evidence that a low lysis value of less than 0.9% at 30 min in the TEG may not reflect shutdown of enzymatic fibrinolysis with hypercoagulability but rather a coagulopathic state of moderate fibrinolysis with fibrinogen consumption and platelet dysfunction that is associated with poor outcomes.[30]

Viewing the available data, it is currently unclear whether the discussed viscoelastic assays can discriminate between different degrees of fibrinolysis or whether test results obtained for clot dissolution are rather an indicator of a general coagulopathy. This may be important for both prognosis and therapeutic decisions and leads to the question of whether the potential of these assays has been fully realized. Timing appears to play a crucial role in fibrinolysis and the narrow therapeutic window. In-vitro and ex-vivo investigations using the tissue factor–activated ROTEM provided convincing evidence that the timing of the onset of lysis, defined as a reduction of clot of more than 15% after the onset of coagulation, provides a faster diagnosis of hyperfibrinolysis than lysis at 30 or 60 min or maximal lysis.[31] Using samples from patients after cardiac arrest, hyperfibrinolysis was diagnosed with the lysis onset time within 7 and 22 min.[31]

The same study showed that functional fibrinogen TEG and fibrinogen ROTEM resulted in the shortest clot lysis time (time from maximal amplitude to 2 mm reduction in viscoelastic amplitude) for the TEG or lysis onset time for the ROTEM system, compared with the other assays.[31] Diagnosis was 1.30 to 2.42 times faster when compared to the other assays. In patients undergoing liver transplantation, the fibrinogen ROTEM assay was shown to have higher sensitivity for detecting hyperfibrinolysis compared to tissue factor–activated ROTEM and kaolin TEG (94% *vs.* 46% and 24%, respectively; $P < 0.001$).[32]

Triggers for Antifibrinolytic Therapy in Clinical Recommendations

In the Society of Cardiac Anesthesiology recommendations, antifibrinolytic therapy is generally suggested for patients undergoing cardiac surgery. However, in patients without prophylactic antifibrinolytic therapy, hyperfibrinolysis should be addressed (table 2).[13] The European trauma guidelines recommend administration of a 1-g bolus of tranexamic acid in trauma patients as soon as possible—preferably before reaching the emergency room—followed by an infusion of 1 g over 8 h, instead of waiting for results of viscoelastic tests.[14] According to the British Society of Haematology, antifibrinolytic therapy in trauma and obstetric patients should not be withheld, based on the results of ROTEM or TEG (table 2).[16]

Future Considerations for Viscoelastic Testing in Bleeding Management

The causes of bleeding, particularly in trauma and cardiac surgery, are mostly multifactorial. Thus, for targeted therapy of diffuse bleeding, reliable information about the major components of the coagulation system is crucial. ROTEM and TEG are widely implemented in modern treatment algorithms.[1,2] However, we believe that further technical considerations in the key assays are necessary. Furthermore, large multicenter studies are needed to validate trigger values for targeted therapeutic interventions (table 3). In view of this, it is also important to investigate the negative predictive value of these tests to rule out a substantial coagulopathy in the bleeding patient. A clear statement in the case of trauma has been published by the British Society of Haematology (table 2).[16] However, a recent meta-analysis highlighted a clear lack of evidence for cardiac surgery.[33]

Future considerations should include minimizing platelet contribution in the fibrinogen assays, because minimal residual platelet noise may have consequences for the decision to transfuse or not transfuse fibrinogen concentrate. All available data show that this can be achieved by dual platelet inhibition in the fibrinogen assays. Further, the question of whether clot amplitude or clot elasticity better signals the contribution of platelets to the clot needs to be answered, because it is perceived that this value is a determinant of platelet function. To date, theoretical considerations are supported by only one study in cardiac surgery and need to be confirmed by additional studies in other clinical settings.[12] This may lead to a fundamental paradigm shift, with clot elasticity used instead of clot amplitude to guide platelet transfusion. In addition, the clotting times of viscoelastic tests should distinguish better between moderate impairment of the clotting system, which can be treated by FFP transfusion alone, and severe impairment, in which hemostatic resuscitation with concentrated clotting factors is indicated instead. To optimize dose and presumably reduce thrombotic complications, these values should serve as a control panel reflecting the effect of these potent clotting factor concentrates. Tissue factor–activated assays that

Table 3. Technical Limitations and Suggested Improvements in Basic TEG/ROTEM Assays

Parameter	Affected Part of the Coagulation System	Assay Specification	Technical Limitations	Data Limitation	Suggested Improvements
Clotting time/ reaction time	Procoagulant factors	Intrinsic activation	Insensitivity for factor VII Longer time until result is achieved when compared to tissue-factor activated assay		
		Extrinsic activation + hexadimethrine bromide for heparin insensitivity < 4 IU/ml			Studies to provide correlation of clotting time with INR Development of trigger values for targeted PCC therapy
Maximum clot firmness/ maximum amplitude	Platelets	Intrinsic activation/extrinsic activation	Platelet effect must be calculated: maximum clot firmness/maximum amplitude total – maximum clot firmness/ maximum amplitude fibrinogen assay Clot elasticity as a better parameter for platelet function: maximum clot elasticity = (maximum clot firmness × 100)/ (100 – maximum clot firmness)	Calculation of platelet contribution to the clot occurs automatically	Studies to provide trigger values for platelet transfusion Clot elasticity needs clinical validation
	Fibrinogen	Intrinsic activation/ extrinsic activation + cytochalasin D or GPIIb/IIIa inhibitor	Potential for residual platelet noise when using single platelet inhibitor		Dual platelet inhibition Recommended thresholds to be confirmed in randomized control trials
Lysis	Thrombolysis		Unclear where performs better: in functional fibrinogen assay or in assay with platelet contribution	Critical values unclear: • Clot lysis at 30 min, 3% or 15% • Lysis onset time	Parameters need to be defined

INR, international normalized ratio; PCC, prothrombin complex concentrate; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

are sensitive to coagulation factor VII appear to have potential in this regard but need further investigation.

For trauma management, rapid assessment of the fibrinolytic system status is an important issue that needs further investigation. The currently used assays that are based on clot lysis often do not correlate with biomarkers of fibrinolysis, including D-dimers, and the parameters and thresholds for hyperfibrinolysis are arbitrarily defined. This might explain the conflicting results in trauma studies regarding the usefulness of viscoelastic tests.[34,35] Therefore, a reevaluation of the thresholds should be considered. There is some evidence that viscoelastic fibrinogen assays, especially those with activated tissue factor, are faster and more sensitive than assays with preserved platelet activity. In addition, clot dissolution time appears to be a parameter that can provide information more rapidly and presumably increase sensitivity for the diagnosis of clinically relevant hyperfibrinolysis.

New devices and new assays have recently been developed for viscoelastic point-of-care testing of the effects of antiplatelet agents and direct oral anticoagulants and assessment of the fibrinolytic system. The ClotPro (Haemonetics, USA) system is almost comparable to ROTEM, but it already applies dual platelet inhibition in its functional fibrinogen assay. The Quantra hemostasis analyzer (Hemosonics, USA) is based on the technique of sonorheometry.[36] First clinical studies provided convincing evidence that the results obtained by this device strongly correlate with results achieved with thromboelastometry and parameters effectively represent results from multiple standard laboratory tests.[37] The setup of activators and tests used is similar to the other discussed viscoelastic test systems, but Quantra already includes an automated calculation of the platelet contribution to the clot stiffness.

Even in light of the development of new diagnostic instruments and a broader line of assays targeting rather specific acquired disturbances of the coagulation system, the basic assays of TEG and ROTEM, including the functional fibrinogen assays, remain the foundation for the vast majority of clinical decisions. In this regard, further improvement and clinical validation of these broadly used basic assays are needed.

Research Support

Competing Interests

Dr. Levy serves on advisory committees for Instrumentation Laboratory, Werfen Company (Bedford, Massachusetts), Merck (Darmstadt, Germany), and Octapharma (Lachen, Switzerland). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Erdoes: Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse, 3010 Bern, Switzerland. gabor.erdoes@insel.ch. Anesthesiology's articles are made freely accessible to all readers on www.anesthesiology.org, for personal use only, 6 months from the cover date of the issue.

References

1. Whiting P, Al M, Westwood M, Ramos IC, Ryder S, Armstrong N, Misso K, Ross J, Severens J, Kleijnen J: Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: A systematic review and cost-effectiveness analysis. Health Technol Assess 2015; 19:1–228

2. Wikkelsø A, Wetterslev J, Møller AM, Afshari A: Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. Cochrane Database Syst Rev 2016; 8:CD007871

3. Dias JD, Sauaia A, Achneck HE, Hartmann J, Moore EE: Thromboelastography-guided therapy improves patient blood management and certain clinical outcomes in elective cardiac and liver surgery and emergency resuscitation: A systematic review and analysis. J Thromb Haemost 2019; 17:984–94

4. Meco M, Montisci A, Giustiniano E, Greco M, Pappalardo F, Mammana L, Panisi P, Roscitano C, Cirri S, Donatelli F, Albano G: Viscoelastic blood tests use in adult cardiac surgery: Meta-analysis, meta-regression, and trial sequential analysis. J Cardiothorac Vasc Anesth 2020; 34:119–27

5. Ranucci M, Baryshnikova E: Sensitivity of viscoelastic tests to platelet function. J Clin Med 2020; 10:189

6. Srivastava A: Diagnosis of haemophilia and other inherited bleeding disorders: Is a new paradigm needed? Haemophilia 2021; 27:14–20

7. Koscielny J, Ziemer S, Radtke H, Schmutzler M, Pruss A, Sinha P, Salama A, Kiesewetter H, Latza R: A practical concept for preoperative identification of patients with impaired primary hemostasis. Clin Appl Thromb Hemost 2004; 10:195–204

8. Schlimp CJ, Solomon C, Ranucci M, Hochleitner G, Redl H, Schöchl H: The effectiveness of different functional fibrinogen polymerization assays in eliminating platelet contribution to clot strength in thromboelastometry. Anesth Analg 2014; 118:269–76

9. Ranucci M, Di Dedda U, Baryshnikova E: Trials and tribulations of viscoelastic-based determination of fibrinogen concentration. Anesth Analg 2020; 130:644–53

10. Olde Engberink RH, Kuiper GJ, Wetzels RJ, Nelemans PJ, Lance MD, Beckers EA, Henskens YM: Rapid and correct prediction of thrombocytopenia and hypofibrinogenemia with rotational thromboelastometry in cardiac surgery. J Cardiothorac Vasc Anesth 2014; 28:210–6

11. Solomon C, Ranucci M, Hochleitner G, Schöchl H, Schlimp CJ: Assessing the methodology for calculating platelet contribution to clot strength (platelet component) in thromboelastometry and thrombelastography. Anesth Analg 2015; 121:868–78

12. Ranucci M, Di Dedda U, Baryshnikova E: Platelet contribution to clot strength in thromboelastometry: Count, function, or both? Platelets 2020; 31:88–93

13. Raphael J, Mazer CD, Subramani S, Schroeder A, Abdalla M, Ferreira R, Roman PE, Patel N, Welsby I, Greilich PE, Harvey R, Ranucci M, Heller LB, Boer C, Wilkey A, Hill SE, Nuttall GA, Palvadi RR, Patel PA, Wilkey B, Gaitan B, Hill SS, Kwak J, Klick J, Bollen BA, Shore-Lesserson L, Abernathy J, Schwann N, Lau WT: Society of Cardiovascular Anesthesiologists clinical practice improvement advisory for management of perioperative bleeding and hemostasis in cardiac surgery patients. J Cardiothorac Vasc Anesth 2019; 33:2887–99

14. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, Komadina R, Maegele M, Nardi G, Riddez L, Samama CM, Vincent JL, Rossaint R: The European guideline on management of major bleeding and coagulopathy following trauma: Fifth edition. Crit Care 2019; 23:98

15. Erdoes G, Koster A, Meesters MI, Ortmann E, Bolliger D, Baryshnikova E, Ahmed A, Lance MD, Ravn HB, Ranucci M, von Heymann C, Agarwal S: The role of fibrinogen and fibrinogen concentrate in cardiac surgery: An international consensus statement from the Haemostasis and Transfusion Scientific Subcommittee of the European Association of Cardiothoracic Anaesthesiology. Anaesthesia 2019; 74:1589–600

16. Curry NS, Davenport R, Pavord S, Mallett SV, Kitchen D, Klein AA, Maybury H, Collins PW, Laffan M: The use of viscoelastic haemostatic assays in the management of major bleeding: A British Society for Haematology guideline. Br J Haematol 2018; 182:789–806

17. de Vries JJ, Veen CSB, Snoek CJM, Kruip MJHA, de Maat MPM: FIBTEM clot firmness parameters correlate well with the fibrinogen concentration measured by the Clauss assay in patients and healthy subjects. Scand J Clin Lab Invest 2020; 80:600–5

18. Bates SM, Weitz JI: Coagulation assays. Circulation 2005; 112:e53–60

19. Tran HT, Tjønnfjord GE, Holme PA: Use of thromboelastography and thrombin generation assay to predict clinical phenotype in patients with severe FVII deficiency. Haemophilia 2014; 20:141–6

20. Erdoes G, Koster A, Ortmann E, Meesters MI, Bolliger D, Baryshnikova E, Martinez Lopez De Arroyabe B, Ahmed A, Lance MD, Ranucci M, von Heymann C, Agarwal S, Ravn HB: A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients. Anaesthesia 2021; 76:381–92

21. Schmidt DE, Chaireti R, Bruzelius M, Holmström M, Antovic J, Ågren A: Correlation of thromboelastography and thrombin generation assays in warfarin-treated patients. Thromb Res 2019; 178:34–40

22. Schmidt DE, Holmström M, Majeed A, Näslin D, Wallén H, Ågren A: Detection of elevated INR by thromboelastometry and thromboelastography in warfarin treated patients and healthy controls. Thromb Res 2015; 135:1007–11

23. Ponschab M, Voelckel W, Pavelka M, Schlimp CJ, Schöchl H: Effect of coagulation factor concentrate administration on ROTEM® parameters in major trauma. Scand J Trauma Resusc Emerg Med 2015; 23:84

24. Longstaff C: Measuring fibrinolysis: From research to routine diagnostic assays. J Thromb Haemost 2018; 16:652–62

25. Moore HB, Moore EE, Neal MD, Sheppard FR, Kornblith LZ, Draxler DF, Walsh M, Medcalf RL, Cohen MJ, Cotton BA, Thomas SG, Leeper CM, Gaines BA, Sauaia A: Fibrinolysis shutdown in trauma: Historical review and clinical implications. Anesth Analg 2019; 129:762–73

26. Walsh M, Shreve J, Thomas S, Moore E, Moore H, Hake D, Pohlman T, Davis P, Ploplis V, Piscoya A, Wegner J, Bryant J, Crepinsek A, Lantry J, Sheppard F, Castellino F: Fibrinolysis in trauma: "Myth," "reality," or "something in between." Semin Thromb Hemost 2017; 43:200–12

27. Raza I, Davenport R, Rourke C, Platton S, Manson J, Spoors C, Khan S, De'Ath HD, Allard S, Hart DP, Pasi KJ, Hunt BJ, Stanworth S, MacCallum PK, Brohi K: The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost 2013; 11:307–14

28. Gall LS, Vulliamy P, Gillespie S, Jones TF, Pierre RSJ, Breukers SE, Gaarder C, Juffermans NP, Maegele M, Stensballe J, Johansson PI, Davenport RA, Brohi K; Targeted Action for Curing Trauma-Induced Coagulopathy (TACTIC) partners: The S100A10 pathway mediates an occult hyperfibrinolytic subtype in trauma patients. Ann Surg 2019; 269:1184–91

29. Moore HB, Moore EE, Liras IN, Gonzalez E, Harvin JA, Holcomb JB, Sauaia A, Cotton BA: Acute fibrinolysis shutdown after injury occurs frequently and increases mortality: A multicenter evaluation of 2,540 severely injured patients. J Am Coll Surg 2016; 222:347–55

30. Cardenas JC, Wade CE, Cotton BA, George MJ, Holcomb JB, Schreiber MA, White NJ; PROPPR Study Group: TEG lysis shutdown represents coagulopathy in bleeding trauma patients: Analysis of the PROPPR cohort. Shock 2019; 51:273–83

31. Dekker SE, Viersen VA, Duvekot A, de Jong M, van den Brom CE, van de Ven PM, Schober P, Boer C: Lysis onset time as diagnostic rotational thromboelastometry parameter for fast detection of hyperfibrinolysis. Anesthesiology 2014; 121:89–97

32. Abuelkasem E, Lu S, Tanaka K, Planinsic R, Sakai T: Comparison between thrombelastography and thromboelastometry in hyperfibrinolysis detection during adult liver transplantation. Br J Anaesth 2016; 116:507–12

33. Woźniak MJ, Abbascianoa R, Monaghana A, Lai FY, Corazari C, Tutino C, Kumar T, Whiting P, Murphy GJ: Systematic review and meta-analysis of diagnostic test accuracy studies evaluating point-of-care tests of coagulopathy in cardiac surgery. Transfus Med Rev 2020; S0887-7963

34. Harr JN, Moore EE, Chin TL, Chapman MP, Ghasabyan A, Stringham JR, Banerjee A, Silliman CC: Viscoelastic hemostatic fibrinogen assays detect fibrinolysis early. Eur J Trauma Emerg Surg 2015; 41:49–56

35. Wang IJ, Park SW, Bae BK, Lee SH, Choi HJ, Park SJ, Ahn TY, Goh TS, Lee MJ, Yeom SR: FIBTEM improves the sensitivity of hyperfibrinolysis detection in severe trauma patients: A retrospective study using thromboelastometry. Sci Rep 2020; 10:6980

36. Baryshnikova E, Di Dedda U, Ranucci M: A comparative study of SEER sonorheometry *versus* standard coagulation tests, rotational thromboelastometry, and multiple electrode aggregometry in cardiac surgery. J Cardiothorac Vasc Anesth 2019; 33:1590–8

37. Groves DS, Welsby IJ, Naik BI, Tanaka K, Hauck JN, Greenberg CS, Winegar DA, Viola F: Multicenter evaluation of the Quantra QPlus system in adult patients undergoing major surgical procedures. Anesth Analg 2020; 130:899–909