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EDITORIAL

Blindspots and limitations in viscoelastic testing in pregnancy

Postpartum hemorrhage (PPH), thrombosis and pulmonary embolism remain the leading causes of maternal morbidity and mortality across the world.[1] In contrast, amniotic fluid embolism (AFE) is a rare clinical entity (1.7–6.6 per 100 000 maternities) characterized by difficulty of diagnosis and quick and often catastrophic changes in hemodynamics (cardiovascular collapse), respiration (respiratory failure) and hemostasis (disseminated intravascular coagulation (DIC) and consumptive coagulopathy). Cases of AFE are associated with high case-fatality rates of 25–50%.[2–5]

Value of viscoelastic testing in acute obstetric hemorrhage

In this issue, Loughran et al. present a case report in which point-of-care ROTEM analysis supported the diagnosis of AFE and guided appropriate hemostatic management.[6] Other reports of decision-making supported by viscoelastic testing (ROTEM or TEG) in this puzzling clinical situation have been published.[7–11]

Viscoelastic testing assesses the dynamics of the mechanical properties of a clot during its initiation, amplification and propagation phases, as well as during subsequent fibrinolysis. In contrast to conventional coagulation tests that are performed in platelet-poor plasma, viscoelastic tests are performed using whole blood and therefore consider the contribution of blood cells to hemostasis according to the cell-based model of hemostasis.[12] The main parameters and assays of ROTEM and TEG are presented in Fig. 1 and Table 1 and further details are published elsewhere.[13]

Pathophysiology of AFE

Amniotic fluid embolism is characterized by intravascular activation and consumption of clotting factors and platelets due to presence of Tissue Factor (TF)-bearing cells in the amniotic fluid. This presents in viscoelastic testing as dose-dependent shortening of coagulation times (CT and CFT in ROTEM and R- and K-time in TEG) in the very early phase of AFE.[14–17] Non-activated viscoelastic assays (NATEM and NA-HEPTEM in ROTEM and non-activated TEG with and without heparinase) are most sensitive to detect TF-bearing cells in blood. These TF-bearing cells cannot be detected by cell-free plasmatic coagulation tests (PT and aPTT).[18] However, minutes later the ensuing consumptive coagulopathy can present as a flat-line in the viscoelastic tests, as seen in the report by Loughran et al.[6] Hyperfibrinolysis in AFE seems to be triggered by cardiovascular collapse rather than by the direct entry and interaction of amniotic fluid with blood.[10,14,15,17,19–21]

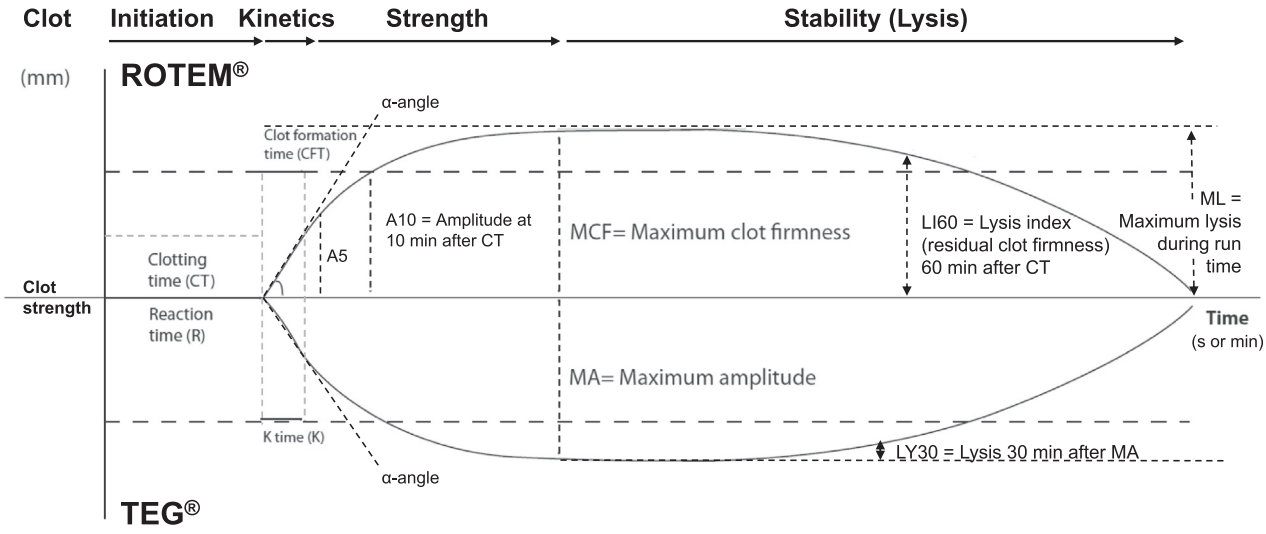
Differential diagnosis of a flat-line temogram and other limitations of viscoelastic testing

The limitations and so-called "blindspots" of viscoelastic testing, particularly with flat-line results as reported initially by Loughran et al.[6], should not be overlooked. It is also important to remember that the limitations can vary depending on the specific technological details and reagents used in various viscoelastic testing devices.

Limitations of viscoelastic testing related to the measuring principle

An overview of blindspots and limitations of viscoelastic testing is provided in Table 2. Viscoelastic tests face challenges in detection of certain coagulation disorders. Since these tests do not work with high shear stress, von Willebrand's disease only affects results if coagulation factor VIII is decreased.[22] Hence, other diagnostic devices with higher shear stress such as the PFA-100 (Siemens Healthcare, Marburg, Germany) are more suitable to screen for von Willebrand's disease.[23] In standard viscoelastic assays, supraphysiologic amounts of thrombin are generated. Thrombin can stimulate platelets by the thrombin-receptors even if the other pathways are blocked by antiplatelet drugs. Accordingly, standard viscoelastic assays are not sensitive to the effects of antiplatelet drugs.[24,25] These issues should be considered in the case of microvascular bleeding in the presence of normal viscoelastic test results. This important limitation has been addressed by TEG Platelet Mapping and ROTEM platelet whole blood impedance aggregometry.[26]

While viscoelastic tests can assess hemostasis in whole blood and detect TF expression on circulating cells such as monocytes and microparticles,[27] they do not assess some of the most important components of hemostasis, for example the vascular endothelium.



	ROTEM®	TEG®	Hemostatic factors
Clot initiation	CT (clotting time) in s	R (reaction time) in min	Enzymatic coagulation factors, anticoagulants, FDPs, tissue factor expression on monocytes
Clot kinetics	CFT (clot formation time) in s α (angle) in degrees	K (kinetic time) in min α (angle) in degrees	Enzymatic coagulation factor, anticoagulants, fibrinogen, platelets
Clot strength	(A5) A10 (amplitude (5) 10 min after CT) in mm MCF (maximum clot firmness) in mm	MA (maximum amplitude) in mm	Platelets, fibrinogen, FXIII, colloids
Clot stability (lysis)	LI60 (lysis index (residual clot firmness) 60 min after CT) in % of MCF ML (maximum lysis during run time) in % of MCF	LY30 (lysis 30 min after MA) in % of MA	Fibrinolytic enzymes, fibrinolysis inhibitors, FXIII

Fig. 1 ROTEM ("temogram") and TEG traces displaying the clinically most important parameters and their informative value. FDPs: fibrin (ogen) split products. Courtesy of Klaus Görlinger[13.]

Endothelium can quickly change from anticoagulant to procoagulant.[28] For example, thrombomodulin is expressed on the membrane of endothelial cells and binds thrombin, acting as an important anticoagulant factor. While some of thrombomodulin molecules may be cleaved and released in plasma, the all-important endothelial fraction is missing and excluded in viscoelastic testing.[29]

Limitations of viscoelastic testing related to assay/reagent composition

A heparin-like effect is mediated by an injury to the endothelial glycocalyx that is induced by severe trauma and shock. This can be detected by heparin-sensitive viscoelastic assays with and without heparinase (INTEM and HEPTEM in ROTEM and kaolin-TEG with and without heparinase cup). A heparin-like effect can often be detected in sepsis, DIC, cirrhosis with infection, liver transplantation and extracorporeal membrane oxygenation (ECMO); and also in severe shock and cardiovascular collapse after trauma, obstetric hemorrhage and AFE.[30–34] Results from viscoelastic assays without a heparin inhibitor can be affected by presence of a heparin-like effect to the extent of a flat-line output.[30,31] The ROTEM liquid reagents (ROTEM delta) and reagent beads (ROTEM sigma) in extrinsically activated assays (EXTEM, FIBTEM and APTEM) contain a heparin-inhibitor which neutralizes up to 5 IU heparin per mL blood. This prevents the prolongation of EXTEM, FIBTEM and APTEM coagulation times (CT and CFT) and decreases early clot firmness amplitudes (A5 and A10) due to exogenous and endogenous heparin effects. This contributes to assay reliability in detecting deficiency of enzymatic coagulation factors of the extrinsic pathway (vitamin K-dependent factors), fibrin polymerization disorders and thrombocytopenia. The single-use reagents for the ROTEM delta assays EXTEM S, FIBTEM S and APTEM S do not contain a heparin inhibitor. Therefore, they must not be used in patients treated with unfractionated heparin (UFH) (e.g. those undergoing cardiovascular surgery or those with therapeutic anticoagulation with UFH) or in patients in whom a significant endogenous liberation of heparinoids (heparin-like effect) can be expected (e.g. after graft reperfusion during liver transplantation, sepsis or hemodynamic shock).[13,35] The same is true for native-TEG, kaolin-TEG, rapid-TEG and TEG Func-

Table 1 ROTEM and TEG assays

ROTEM assay (reagent composition)	TEG assay (reagent composition)	Clinical implication
INTEM ($CaCl_2$ + ellagic acid)	Kaolin-TEG ($CaCl_2$ + kaolin)	Deficiency of factors of the intrinsic pathway Detection of unfractionated heparin (UFH) and protamine effects (in combination with HEPTEM or Heparinase-Kaolin-TEG)
HEPTEM ($CaCl_2$ + ellagic acid + heparinase)	Heparinase-Kaolin-TEG ($CaCl_2$ + kaolin + heparinase)	Testing in patients with high heparin plasma concentrations. Detection of UFH and protamine effects (in combination with INTEM or Kaolin-TEG)
EXTEM ($CaCl_2$ + tissue factor + polybrene)	Rapid-TEG ($CaCl_2$ + kaolin + tissue factor)	Deficiency of factors of the extrinsic pathway Detection of vitamin K-antagonists Indication for FFP or PCC administration
FIBTEM ($CaCl_2$ + tissue factor + polybrene + cytochalasin D)	TEG Functional Fibrinogen ($CaCl_2$ + kaolin + tissue factor + GPIIbIIIa receptor antagonist)	Detection of fibrin polymerisation issues Dose calculation for fibrinogen concentrate or cryoprecipitate
APTEM ($CaCl_2$ + tissue factor + polybrene + aprotinin/tranexamic acid)	No corresponding TEG assay available	Verifying the effect of antifibrinolytic drugs Differential diagnosis between hyperfibrinolysis and platelet-mediated clot retraction (in combination with EXTEM)
NATEM ($CaCl_2$)	Native TEG ($CaCl_2$)	Detection of tissue factor expression on monocytes Other anticoagulants (e.g., LMWH; in combination with NA-HEPTEM or native TEG with heparinase)
NA-HEPTEM ($CaCl_2$ + heparinase)	Native TEG with heparinase ($CaCl_2$ + heparinase)	Detection of tissue factor expression on monocytes in blood samples with a (potential) heparin-like effect

LMWH: low-molecular weight heparin; FFP: fresh frozen plasma; PCC: prothrombin complex concentrate.

Table 2 Blindspots and limitations of viscoelastic testing

Blindspots and limitations based on the measuring principle of viscoelastic testing	Blindspots and limitations based on assay/reagent composition
Von Willebrand's disease	Heparin-like effect
Detection of platelet dysfunction	Hyperfibrinolysis
Detection of endotheliopathy	Vitamin K-antagonists and direct oral anticoagulants (DOACs)

tional Fibrinogen assay if not performed in a heparinase cup. Therefore, TEG analysis after liver graft reperfusion or during ECMO can result in a flat-line thromboelastograph in 27–46% of cases, reversed by using a heparinase cup.[30,33] This possibility has to be considered for choosing the right assay and doing a correct interpretation of test results in these settings.

Hyperfibrinolysis is mediated by a mismatch between increased tissue plasminogen activator release from activated endothelial cells and decreased availability of fibrinolysis inhibitors (plasminogen activator inhibitor-1 [PAI-1] and alpha$_2$-antiplasmin), due to inactivation by activated protein C or thrombocytopenia.[36,37] There is an ongoing debate whether viscoelastic testing is sensitive enough to detect low-grade hyperfibrinolysis and as to which laboratory test should be considered the gold standard for detecting hyperfibrinolysis.[38–41] Furthermore, there are different terms in use to describe a dysregulation in fibrinolysis: (clinical) hyperfibrinolysis, (endogenous) fibrinolytic activation, physiologic fibrinolysis, hypofibrinolysis and fibrinolysis shutdown.[21,39,42,43] Raza et al. concluded that conventional ROTEM (EXTEM) is insensitive to "endogenous fibrinolytic activity."[41] However, in this study arbitrary cut-off values for EXTEM maximum lysis (ML) and plasmin antiplasmin (PAP) complexes were used, and corresponding half-life times were not considered. Accordingly, PAP complexes do not allow for assessing the efficacy of antifibrinolytic therapy. In contrast, in vitro testing of the efficacy of antifibrinolytic therapy can be done using ROTEM with an extrinsically activated assay which includes aprotinin (APTEM) or tranexamic acid (tAPTEM).[19,38,44,45] The APTEM assay can also be used in comparison to EXTEM to discrim-

inate between hyperfibrinolysis and platelet-mediated clot retraction since the latter is not corrected by APTEM.[38,46] It has been shown in trauma and sepsis patients that EXTEM LI60 values can be used to distinguish between hyperfibrinolysis, physiologic fibrinolysis and fibrinolysis shutdown,[43,47] which is associated with increased mortality due to organ failure.[21] Cut-off values for hyperfibrinolysis have been established by receiver operating characteristics (ROC) curve analysis to predict massive transfusion or death within six hours and for fibrinolysis shutdown to predict mortality in the patient population without hyperfibrinolysis.[45] The sensitivity of viscoelastic tests for detection of hyperfibrinolysis is strongly dependent on the cut-off values used.[48] Furthermore, Abuelkasem et al. and Harr et al. independently demonstrated that FIBTEM is much more sensitive and specific for hyperfibrinolysis than are kaolin-TEG and EXTEM.[49,50] Since platelets are blocked in FIBTEM, platelet-mediated clot retraction does not occur and alpha$_2$-antiplasmin cannot be incorporated by factor XIII into the clot.[46,51] Further studies are needed to identify which viscoelastic tests are most sensitive to examine fibrinolysis associated with PPH and to characterize the impact of thrombocytopenia and hypofibrinogenemia on the progression of PPH.[52]

Notably, severe hyperfibrinolysis can also result in a flat-line thromboelastogram in ROTEM or TEG – in particular in combination with a heparin-like effect and consumption coagulopathy.[30,53] The APTEM is the only viscoelastic assay available which eliminates both a heparin-like effect and hyperfibrinolysis and allows for adequate assessment of coagulation time and clot firmness amplitude under these conditions.[13,38] Accordingly, it is essential to run an APTEM test in case of a flat-line ROTEM if the patient has not been treated with an antifibrinolytic drug, as described in the case report by Loughran et al.[6]

Other reasons for a flat-line TEG or ROTEM as reported by Loughran et el.[6] can be technical errors (e.g., empty star-tem vial), citrate intoxication due to excessive plasma transfusion in severe bleeding[54] and performing a TEG on native blood (non-citrated). Using native blood samples, TEG analysis has to be started within three minutes of blood sampling. Otherwise, the blood sample might already have clotted – in particular in cases with TF expression on circulating cells such as in sepsis, liver transplantation, ECMO and AFE – and may not clot again during analysis.[14,17,27,47]

Knowledge about the blindspots and limitations of viscoelastic testing is important for the correct selection of assays performed in challenging and potentially fatal clinical situations, such as PPH, AFE, and DIC, and for appropriate interpretation of the results. This will ensure that viscoelastic testing supports clinicians to make correct diagnostic and therapeutic decisions in a timely manner. In this context, thromboelastometry-guided algorithms are recommended in clinical guidelines to support hemostasis management in PPH.[55–60]

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