Whole Blood Assay: Thromboelastometry – Basics

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Klaus Görlinger, James Iqbal, Daniel Dirkmann, and Kenichi A. Tanaka

Thromboelastometry Devices, Assays, and Parameters

The ROTEM™ Devices

Rotational thromboelastometry (ROTEM™, Tem Innovations GmbH, Munich, Germany, and Instrumentation Laboratory, Bedford, MA, USA) is a whole blood viscoelastic hemostasis analyzer, which evolved from the original thrombelastography (TEG) system, introduced by Hellmut Hartert in 1948, in the 1990s by Andreas Calatzis to the ROTEG™ and later ROTEM™ system [1, 2]. Although the TEG™ 5000 and ROTEM™ *delta* devices still share similarities, there are several distinct differences with regard to measurement technique, assays, and measurement variables (Table 6.1).

The ROTEM™ *delta* device (Fig. 6.1a, b) consists of a compact measurement unit with four temperature-adjusted independent measurement channels, a pre-warming plate, a reagent tray, and an integrated personal computer, allowing for remote viewing and LIS (laboratory information system) connection. An attached touch screen and a software-assisted, automatic pipette are used to control the device and the specific ROTEM™ software. This makes the device very user-friendly and reduces intra- and inter-operator variability of test results [7] and allows for using the device in a multiuser environment, e.g., in the emergency room (ER), in the operating room (OR), or at the intensive care unit (ICU). Furthermore, the user is guided through the measurement process by the ROTEM™ device with instructions and pictograms, displayed on the touch screen, and a help menu can be activated if support in result interpretation is desired. Of course, this does not substitute for adequate education in hemostasis and decision-making by the attending physician.

The ROTEM™ *delta* device is complemented by the ROTEM™ *platelet* device (Fig. 6.1a, c–e), CE-marked (certification mark) in Europe since November 2013, which provides platelet function analysis based on the well-established whole blood "impedance aggregometry" or "multiple electrode aggregometry" technology (more than 600 hits in PubMed) [44–51]. Together, ROTEM™ *delta* and ROTEM™ *platelet* provide six measuring channels, four channels for viscoelastic testing and two channels for platelet function analysis.

Finally, the new fully automated ROTEM™ *sigma* device (Fig. 6.1f, g) is a cartridge-based system (with four channels), CE-marked in Europe since August 2015 (FDA validation studies are running), working with lyophilized reagent beads but still with the proven cup-and-pin technology. With the ROTEM™ *sigma* device, pipetting is no longer required, which significantly increases user-friendliness and reproducibility of the results [53].

Measurement Technique

The four independent viscoelastic measurement channels of the ROTEM™ *delta* device allow for using a panel of specific assays. This improves the diagnostic performance of the device compared to a mono-assay system activated by kaolin [13–15, 37–41]. Accordingly, the ROTEM™ *delta* device is suitable not only to detect a coagulopathy in real time but

K. Görlinger (✉)
Department of Anesthesiology and Intensive Care Medicine, University Hospital Essen, Essen, Germany

Tem Innovations GmbH, Munich, Germany
e-mail: kgoerlinger@ilww.com

J. Iqbal
Department of Pathology and Laboratory Medicine, James J. Peters VA Medical Center, Bronx, NY, USA

D. Dirkmann
Department of Anesthesiology and Intensive Care Medicine, University Hospital Essen, Essen, Germany
e-mail: daniel.dirkmann@uk-essen.de

K. A. Tanaka
Department of Anesthesiology, Division of Cardiothoracic Anesthesiology, University of Maryland Medical Center, Baltimore, MD, USA
e-mail: ktanaka@anes.umm.edu

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Table 6.1 Characteristics and performance of thrombelastography (TEG™) and thromboelastometry (ROTEM™)

Characteristics and performance	TEG™ 5000	ROTEM™ *delta*
Mechanical robustness, susceptibility to artifacts [3–6]	Cup is moving and clot firmness is detected by a torsion wire with high susceptibility to agitation and movement artifacts limiting its mobile use at the bedside; therefore, TEGs are most often located in the central laboratory	Cup is fixed and pin is moving; stabilization of the pin axis by a ball bearing and contactless optical detection of the pin movement result in low susceptibility to agitation and movement artifacts; this enables bedside testing and mobile use – even in military settings
Pipetting and reproducibility of results [7]	Manual pipetting results in higher intra- and inter-operator variability of test results	Software-assisted automatic pipette is user-friendly and results in low intra- and inter-operator variability of the results and enables a multiuser environment with bedside testing in the ER, OR, and ICU
Quality control (QC) [4, 8]	No continuous electronic QC; therefore, QC with control reagents is at least once a day (based on the local regulations in some places even every 8 h) required	Continuous electronic QC of the pin axis movement; therefore, QC with control reagents is only once a week required; this results in reduced staff workload and QC costs
Number of channels for viscoelastic testing [2–4]	2 channels per device (if TEG® platelet mapping is performed, channels are blocked for other viscoelastic testing)	4 channels per device (the ROTEM® *platelet* module provides two additional channels for impedance aggregometry)
Viscoelastic assays [9–15]	5 different assays (native TEG, kaolin-TEG, heparinase-TEG, rapid-TEG, TEG functional fibrinogen (FF)); only heparinase-TEG can be used already during cardiopulmonary bypass (CPB)	8 different assays (NATEM, NA-HEPTEM, INTEM, HEPTEM, EXTEM, FIBTEM, APTEM, ECATEM); tissue factor-activated assays (EXTEM, FIBTEM, APTEM) contain a heparin inhibitor and can – as well as HEPTEM – already be used during CPB
Preferred activation pathway [9, 16–27]	Intrinsic pathway (kaolin); poor correlation to the effect of oral vitamin K antagonists and prothrombin complex concentrate (PCC)	Extrinsic pathway (tissue factor); good correlation to the effect of oral vitamin K antagonists, direct oral anticoagulants (DOACs), and prothrombin complex concentrate (PCC)
Turnaround time [6, 11, 13, 28–35]	Reference range for r-time in kaolin-TEG 4–8 min; no early variables of clot firmness available; turnaround time 25–45 min	Reference range for EXTEM 40–80 s; early variables of clot firmness (A5 and A10) are validated and predict MCF accurately; turnaround time 10–15 min
Definition of lysis parameters [36]	LY30/LY60 (lysis 30/60) is defined as the reduction of clot firmness *30/60 min after MA* in percentage of MA	LI30/LI60 (lysis index 30/60) is defined as residual clot firmness *30/60 min after CT* in percentage of MCF
Diagnostic performance [13–15, 37–43]	Poor discrimination between fibrinogen deficiency and thrombocytopenia; most often used to predict bleeding rather than to guide hemostatic therapy	Improved diagnostic performance based on test combinations; good discrimination between fibrinogen deficiency and thrombocytopenia; enables guided therapy with allogeneic blood products and coagulation factor concentrates ("theranostic approach" in precision medicine)
Platelet function analysis [44–51]	TEG™ platelet mapping (PM); viscoelastic channels are blocked during TEG™ PM; test principle is based on the use of reptilase + FXIIIa + arachidonic acid (AA) or adenosine diphosphate (ADP); long turnaround time, high costs, and high variability of the results	ROTEM™ *platelet* module provides two additional channels for whole blood impedance aggregometry; platelet activation with AA (ARATEM), ADP (ADPTEM), or thrombin receptor-activating peptide (TRAPTEM); short turnaround time (10 min), good reproducibility of the results, and good correlation to clinical outcomes
Fully automated system [52, 53]	TEG™ 6S (CORA™ system); cartridge-based system using a new technology based on coagulation resonance analysis (CORA); interchangeability of TEG™ 5000 and TEG™ 6S (CORA™) results has to be investigated	ROTEM™ *sigma*; cartridge-based system using the proven pin-and-cup technology but lyophilized beads reagents instead of liquid reagents; ROTEM™ *sigma* beads contain a heparin inhibitor as the liquid reagents do

Courtesy of Klaus Görlinger, Essen, Germany
ER emergency room, *ICU* intensive care unit, *OR* operating room

also to differentiate between different causes of coagulopathies, e.g., between hypofibrinogenemia and thrombocytopenia, and is designed to guide hemostatic therapy in bleeding patients [32, 54–61]. Each measurement channel consists of a disposable cuvette fixed in a temperature-adjusted metal cup holder and a disposable pin attached to a moving axis, stabilized by a ball bearing. The ROTEM™ axis is alternatingly rotating forth and back by 4.75° 12 times per minute. After starting the test by re-calcifying the citrated whole blood in the cup and adding an activator (tissue factor, ellagic acid, or ecarin), clot strands between pin and cup wall are increasingly impairing the pin rotation. These changes in pin movement are detected by a LED light-mirror-light detector system, and the consequential signal is processed and transformed by the integrated computer into a thromboelastometric curve (TEMogram), finally (Fig. 6.1b). In addi-

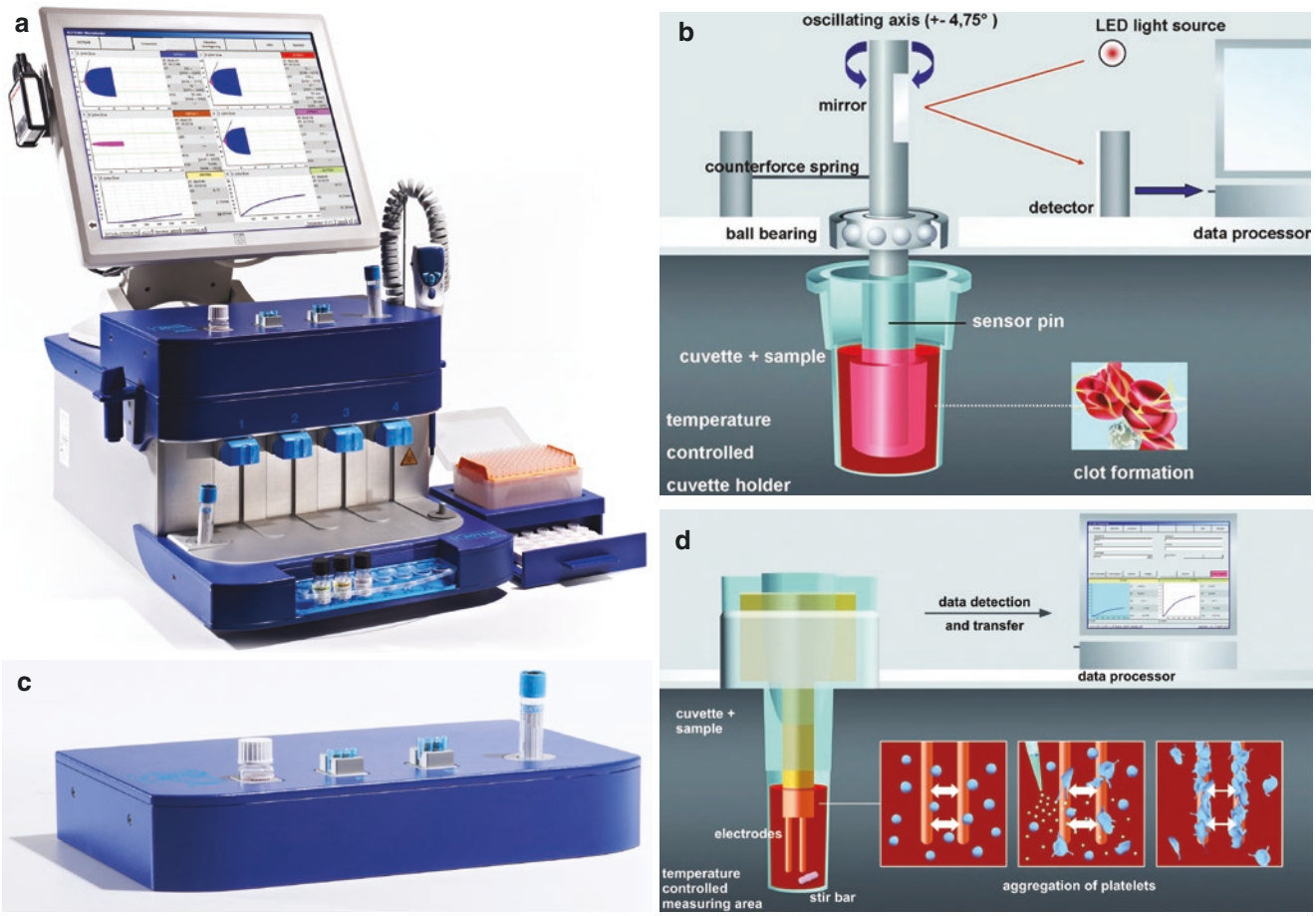


Fig. 6.1 (**a**–**g**) ROTEM™ devices. (**a**) ROTEM™ *delta* device (thromboelastometry) plus ROTEM™ *platelet* module (whole blood impedance aggregometry); (**b**) ROTEM™ *delta* measuring principle; (**c**) ROTEM™ *platelet* module; (**d**) ROTEM™ *platelet* measuring principle; (**e**) ROTEM™ *platelet* measuring curve and parameters (MS = maximum slope in Ohm/min; A6 = amplitude at 6 min in Ohm; AUC = area under the aggregation curve in Ohm*min); (**f**) ROTEM™ *sigma* fully automated device; (**g**) ROTEM™ *sigma* cartridge type 1 (C cartridge ROTEM™ assay) (Courtesy of Klaus Görlinger, Tem Innovations, Munich, Germany)

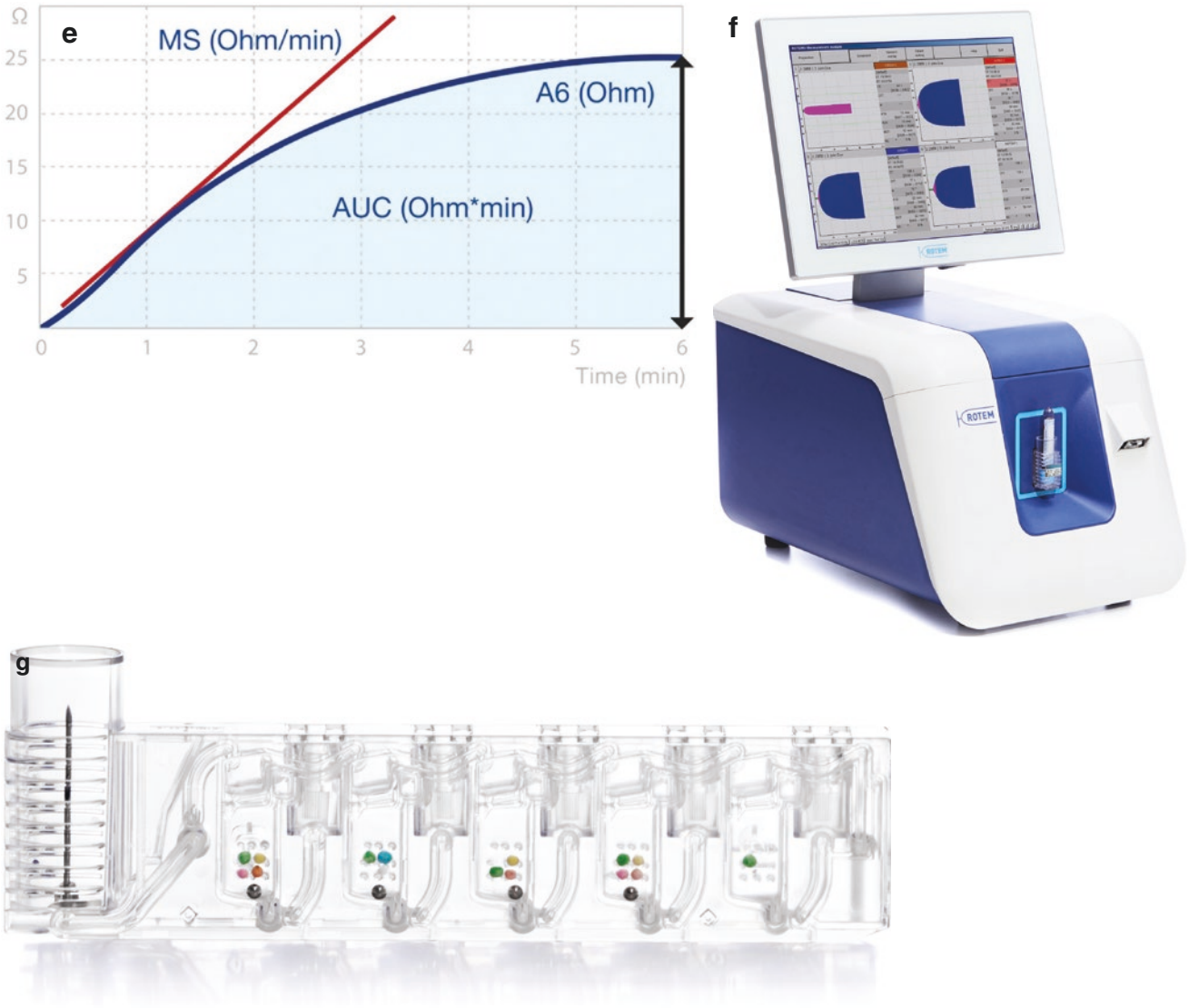


Fig. 6.1 (continued)

tion, specific ROTEM™ parameters are calculated by the computer and displayed on the touch screen in real time. These technical modifications make the ROTEM™ *delta* device on the one hand less susceptible to vibrations and movement artifacts and, on the other hand, allow for a continuous electronic quality control of the pin movement. Therefore, quality control using the reagents ROTROL™ N and P is necessary only once a week, compared to daily QCs required for other viscoelastic test devices such as the TEG™ device [4, 8]. This reduces costs and workload significantly [8]. Furthermore, the device can be used in a mobile way at the bedside (e.g., in the ER, OR, ICU, or a satellite laboratory) and can even be moved around with the patient on a customized trolley providing uninterrupted power supply (Table 6.1). Accordingly, ROTEM™ *delta* devices have successfully been used in military settings and other outdoor environments (e.g., mountaineering in the Himalaya and the Andes) [5, 6].

The ROTEM™ *sigma* device actually works with two different cartridges (Fig. 6.1g), providing four channels each (cartridge type 1, FIBTEM C, EXTEM C, INTEM C, APTEM C; cartridge type 2, FIBTEM C, EXTEM C, INTEM C, HEPTEM C; here C stands for cartridge) [53].

ROTEM™ Assays

Thromboelastometric assays use citrated whole blood (300 µL per assay), which is re-calcified and activated by tissue factor (extrinsic pathway), ellagic acid (intrinsic pathway), or ecarin (direct prothrombin activation). Some assays contain further additives (Table 6.2). In contrast to the TEG™ system, all pipetting steps are guided by the ROTEM™ software and performed using a software-driven ROTEM™ *delta* pipette. This allows for improved multiuser handling with lower intra- and inter-operator variability of the results when compared to other viscoelastic testing devices [3–5]. The ROTEM™ system provides various activated assays which in combination considerably improve the diagnostic performance of the device in comparison to a mono-assay system [37–39]. Up to four viscoelastic tests can be performed and displayed on the touch screen, simultaneously (Fig. 6.1a). Here, extrinsically activated assays (EXTEM, FIBTEM, and APTEM), intrinsically activated assays (INTEM and HEPTEM), an ecarin-activated assay (ECATEM), and two nonactivated assay (NATEM and NA-HEPTEM) are available. A new preparation of ECATEM is under development.

Similar to the prothrombin time, the *EXTEM* assay is activated by re-calcification (star-tem™ reagent, containing 0.2 mol/L calcium chloride) and addition of tissue thromboplastin (r ex-tem™ reagents, i.e., recombinant tissue factor and phospholipids). Accordingly, since coagulation is initiated through the extrinsic pathway, initial thrombin generation and hence initial clotting mainly depends on the activity of the coagulation factors VII, X, V, II, and I (fibrinogen) in EXTEM test. EXTEM CT can be used to guide FFP and PCC administration in patients suffering from bleeding due to vitamin K-dependent factor deficiency, e.g., due to warfarin therapy [17–23]. Prolonged EXTEM CT should only be used for clinical decision-making in the presence of sufficient amounts of fibrinogen (normal FIBTEM A5 or A10), since severe hypofibrinogenemia often results in prolonged EXTEM and FIBTEM CT. EXTEM and FIBTEM CT are also sensitive but

Table 6.2 ROTEM™ *delta* (*sigma*) and ROTEM™ *platelet* assays

Assay	Activators and additives	Clinical comments
ROTEM™ *delta* assays		
EXTEM	$CaCl_2$ + recombinant tissue factor + polybrene	Deficiency of factors of the extrinsic pathway; VKAs and DOACs; indication for PCC administration
FIBTEM	$CaCl_2$ + recombinant tissue factor + polybrene + cytochalasin D	Fibrin polymerization; dose calculation for fibrinogen concentrate or cryoprecipitate; hyperfibrinolysis; FXIII deficiency
APTEM	$CaCl_2$ + recombinant tissue factor + polybrene + aprotinin/ tranexamic acid	Verifying the effect of antifibrinolytic drugs; differential diagnosis to clot retraction and FXIII deficiency (in combination with EXTEM)
INTEM	$CaCl_2$ + ellagic acid	Deficiency of factors of the intrinsic pathway; unfractionated heparin (UFH) and protamine effects (in combination with HEPTEM)
HEPTEM	$CaCl_2$ + ellagic acid + heparinase	Testing in patients with very high heparin plasma concentrations; UFH and protamine effects (in combination with INTEM)
NATEM	$CaCl_2$	Tissue factor expression on circulating cells (e.g., monocytes or malignant cells); other anticoagulants (e.g., LMWH)
NA-HEPTEM	$CaCl_2$ + heparinase	Tissue factor expression on circulating cells (e.g., monocytes or malignant cells) in blood samples with heparin or HLE; other anticoagulants (e.g., LMWH) (in combination with NATEM)
ECATEM	$CaCl_2$ + ecarin	Direct thrombin inhibitors (e.g., hirudin, argatroban, bivalirudin, dabigatran); not sensitive to heparin; new preparation under development
ROTEM™ *platelet* assays		
ARATEM	Arachidonic acid (AA)	COX-1 (e.g., aspirin) and GPIIbIIIa receptor inhibitor effects; effects of CPB, trauma, and sepsis
ADPTEM	Adenosine diphosphate (ADP)	ADP (P2Y12) (e.g., clopidogrel and prasugrel) and GPIIbIIIa receptor inhibitor effects; effects of CPB, trauma, and sepsis
TRAPTEM	Thrombin receptor-activating peptide-6 (TRAP-6)	Thrombin (PAR-1) (e.g., vorapaxar) and GPIIbIIIa receptor inhibitor effects; effects of CPB, trauma, and sepsis

Courtesy of Klaus Görlinger, Essen, Germany
ADP adenosine diphosphate, *COX-1* cyclooxygenase-1, *CPB* cardiopulmonary bypass, *DOACs* direct oral anticoagulants, *HLE* heparin-like effect, *LMWH* low molecular weight heparin, *PAR-1* protease-activated receptor-1, *PCC* protamine complex concentrate, *UFH* unfractionated heparin, *VKAs* vitamin K antagonists

not specific to the effect of direct oral anticoagulants (DOACs) such as dabigatran and rivaroxaban [24–27]. Furthermore, early variables of clot firmness (A5 and A10) in EXTEM can be used for early detection of fibrinolysis [33].

The *FIBTEM* assay consists of a modified EXTEM assay with addition of a potent platelet inhibitor (cytochalasin D), which blocks platelet activation, shape change, and expression and activation of glycoprotein IIb/IIIa, which is a fibrin(ogen) receptor [62]. Thereby, platelet contribution to clot formation and clot strength is eliminated in this assay [38]. Accordingly, clot strength in FIBTEM is based on fibrinogen concentration and fibrin polymerization solely, whereas clot strength in EXTEM depends on platelet count, platelet function, fibrinogen concentration, and fibrin polymerization. Therefore, the combination of EXTEM and FIBTEM allows for discrimination between thrombocytopenia or platelet dysfunction and hypofibrinogenemia [39, 58, 61]. The difference in clot strength between EXTEM and FIBTEM allows for estimation of the platelet part of clot firmness (referred as PLTEM by some authors) [13, 54, 63, 64]. FIBTEM is also sensitive to factor XIII deficiency ($r = 0.60$) [65–68]. Furthermore, recent studies have shown that FIBTEM is the most sensitive and specific assay for the detection of hyperfibrinolysis compared to kaolin-TEG and EXTEM [69, 70].

A third extrinsically activated assay – the *APTEM* test – includes an antifibrinolytic drug (in the past aprotinin and nowadays tranexamic acid (t ap-tem™)) allowing for in vitro assessment of an antifibrinolytic therapy. Furthermore, the test combination of EXTEM and APTEM allows for the discrimination between fibrinolysis and other reasons for clot instability, such as platelet-mediated clot retraction and factor XIII deficiency [71–74]. The latter ones cannot be blocked by an antifibrinolytic drug and therefore are still present in APTEM. Notably, FIBTEM can also be used for the discrimination between fibrinolysis and platelet-mediated clot retraction since platelet function is blocked in this assay. All extrinsically activated liquid assays contain polybrene, a heparin inhibitor which allows for immediate elimination of heparin effects (up to 5 units unfractionated heparin per mL). This enables the use of these tests even in heparin-treated patients, e.g., during cardiopulmonary bypass [9–15].

The *INTEM* assay is activated by re-calcification and addition of ellagic acid and phospholipids. Due to the intrinsic activation, similar to the activated partial thromboplastin time, initial thrombin generation and clot formation in INTEM mainly depends on coagulation factors XII, XI, IX, VIII, X, V, and II and I (fibrinogen) [58]. As in EXTEM, clot firmness reflects both platelet and fibrin contribution to the clot. In contrast to all extrinsically activated assays, INTEM does not contain a heparin inhibitor. However, a modified INTEM assay, containing additional heparinase (*HEPTEM*; eliminates up to 10 IU/mL), can be used in combination with INTEM in order to reveal (residual) heparinization or protamine overdose [75–77]. The INTEM/HEPTEM CT ratio correlates well with anti-Xa activity ($r = 0.72$) [78].

The *ECATEM* assay uses the viper venom ecarin as an activator. Ecarin directly converts prothrombin to meizothrombin which has already a low level of thrombin activity. Crucially, meizothrombin is inhibited by hirudin and other direct thrombin inhibitors (such as argatroban, bivalirudin, and dabigatran), but not by heparin [79–81]. Other than in prothrombin deficiency, the clotting time in ECATEM is unaffected by other enzymatic coagulation factor deficiencies, by Coumadin (warfarin), by direct factor Xa inhibitors (such as rivaroxaban, apixaban, and edoxaban), or by the presence of phospholipid-dependent anticoagulants (such as lupus anticoagulant). The eca-tem™ reagent is approved in Europe only, and a new preparation with better stability is under development [82].

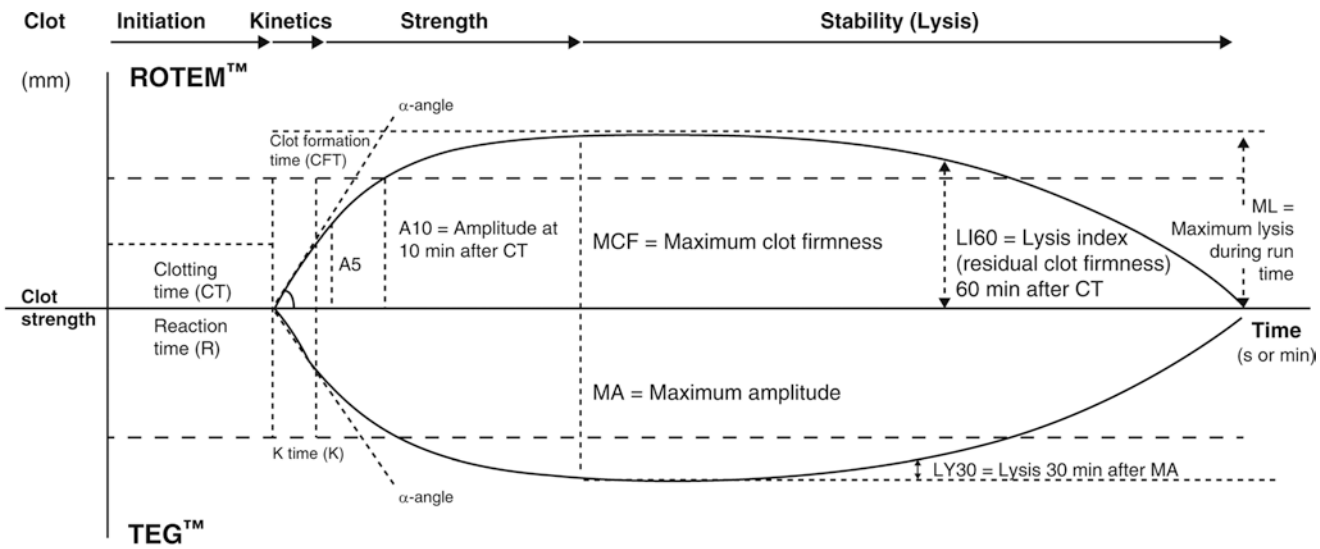
The *NATEM* assay is activated by re-calcification (star-tem® reagent) only. The test is very sensitive to any endogenous activator such as tissue factor expression on circulating monocytes in infection, sepsis, liver cirrhosis, or malignancies and in patients treated with extracorporeal assist devices [73, 83–86]. Therefore, this assay may be helpful to detect a pathophysiological change from trauma-induced coagulopathy (TIC) to disseminated intravascular coagulopathy (DIC). Finally, the *NA-HEPTEM* assay, which contains heparinase in addition to $CaCl_2$, eliminates a potential heparin effect. This avoids an interference with heparin due to prophylactic or therapeutic anticoagulation with heparin or due to an endogenous heparin-like effect (HLE) [73, 83–89], in patients in whom tissue factor expression on circulating cells should be detected. Furthermore, the NATEM/NA-HEPTEM CT ratio is very sensitive to unfractionated (UFH) and low molecular weight (LMWH) heparin [90]. Besides the standard liquid reagents, lyophilized single-potion or *single-use reagents (SURs)* are available in Europe and several other countries [91]. Since SURs contain all reagents needed for one assay, lyophilized in one vial, pipetting is minimized to adding 300 µL of citrated whole blood to the reagent vial and transferring the activated blood 5 s later to the ROTEM™ cup. SURs are labeled by the suffix S (e.g., ex-tem™ S), which is also displayed on the ROTEM™ *delta* screen when SURs have been used for the analysis. Notably, extrinsically activated SURs do not contain a heparin inhibitor and, therefore, must not be used in patients treated with UFH (e.g., in cardiac and vascular surgery or in patients with therapeutic anticoagulation with UFH) as well as in patients in which a significant endogenous liberation of heparinoids can be expected (e.g., after graft reperfusion in liver transplantation or after severe hemorrhagic shock). UFH can result in prolonged CT and CFT as well as in reduced clot firmness (A-values and MCF) by using SURs in these settings. A heparin effect can be verified by the test combination INTEM (S) and HEPTEM (S).

ROTEM™ Parameters

The ROTEM™ test results are characterized by several ROTEM™ parameters. Besides the standard ROTEM™ parameters, several other parameters are used for research only (Fig. 6.2, Table 6.3, and ROTEM™ *delta* manual) [92–95]. ROTEM™ *reference ranges* can slightly vary from country to country (e.g., between Europe and the USA) and even from hospital to hospital. Therefore, these reference ranges are for orientation only, and it is recommended to establish hospital-specific reference ranges. Here, the reference population, age, blood sampling vials and technique, sample transport, and other pre-analytic factors may affect the results. Notably, specific age-related reference ranges for *infants/children* and trimester-related reference ranges for *pregnant woman* have been published, too [53, 96–103].

Clot Initiation and Amplification Parameters (Clot Kinetics)

The thromboelastometric coagulation time (*CT*) in seconds corresponds to the reaction time (*r*) of TEG™ assays. In ROTEM™ assays, CT is defined as the time from test start until a clot firmness amplitude of 2 mm is reached. In tissue factor-activated tests, the CT is usually achieved within about 1 min. The CT reflects the speed of thrombin generation and is mainly affected by the enzymatic activity of coagulation factors (extrinsic or intrinsic, depending on the assay used), the concentration of anticoagulants and fibrin split products, as well as tissue factor expression on circulating cells (e.g., monocytes or malignant cells) [73, 83–85]. EXTEM CT is a reliable indicator of sepsis-induced DIC, diagnosed by the Japanese Association for Acute Medicine (JAAM) DIC score, and is strongly associated with severity of DIC [104]. Furthermore, EXTEM CT can be used to guide FFP and PCC administration in patients suffering from bleeding due to vitamin K-dependent factor deficiency, e.g., due to warfarin therapy, liver insufficiency, and trauma [17–23, 105]. In contrast to INTEM CT as well as kaolin-TEG and rapid-TEG R-time, EXTEM CT correlates well with INR in patients treated with vitamin K antagonists (r = 0.87) [16–18]. However, EXTEM CT is superior in predicting bleeding complications compared to international normalized ratio (INR) in several other settings such as liver cirrhosis and infection/sepsis. Thereby,



	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. 6.2 ROTEM™ ("temogram") and TEG™ trace displaying the clinically most important parameters and their informative value. *FDPs* fibrin(ogen) split products (Courtesy of Klaus Görlinger, Essen, Germany)

Table 6.3 ROTEM™ *delta* (*sigma*) parameters

Acronym	Parameter	Unit	Definition
Coagulation activation and clot polymerization parameters			
CT	Coagulation time	s	Time from test start until a clot firmness amplitude of 2 mm is reached
CT-ratio	Coagulation time ratio	–	For example, INTEM CT/HEPTEM CT in order to quantify a heparin effect
CFT	Clot formation time	s	Time between 2 and 20 mm clot firmness amplitude is achieved
α	Alpha-angle	degree (°)	Angle between the baseline and a tangent to the clotting curve through the 2 mm point
Clot firmness parameters			
A5	Amplitude at 5 min	mm	Amplitude of clot firmness 5 min after CT
A10	Amplitude at 10 min	mm	Amplitude of clot firmness 10 min after CT
A20	Amplitude at 20 min	mm	Amplitude of clot firmness 520 min after CT
MCF	Maximum clot firmness	mm	Maximum amplitude of clot firmness reached during the runtime
PLTEM A5 (A10, MCF)	Platelet contribution to clot firmness	mm	EXTEM A5 (A10, MCF) – FIBTEM A5 (A10, MCF)
Clot lysis parameters			
ML	Maximum lysis	%	Maximum lysis detected during the runtime, described in % of MCF
LI30	Lysis index at 30 min	%	Residual clot firmness at 30 min after CT, described in % of MCF
LI60	Lysis index at 60 min	%	Residual clot firmness at 60 min after CT, described in % of MCF
LOT	Lysis onset time	s	Time from CT until clot firmness is decreased by 15% as compared to the MCF
ROTEM™ *delta* research parameters			
MCE	Maximum clot elasticity	–	MCE = 100 x MCF / (100 – MCF)
G	Shear elastic modulus strength	–	G = 5000 x MCF / (100 – MCF)
TPI	Thrombodynamic potential index	s^{-1}	TPI = MCE / CFT
LT	Lysis time	s	Time from CT until the clot firmness is decreased to 10% as compared to the MCF
CLR	Clot lysis rate	degree (°)	Angle between the baseline and the tangent to the declining clot firmness curve
ROTEM™ *delta* research parameters for the first derivative curve (Sørensen 2003)			
maxV	Maximum velocity	mm/min	Maximum of the first derivative of the curve
maxV-t	Time to maximum velocity	s	Time from test start until the maximum of the first derivative of the curve is reached
AUC	Area under the curve	mm × min	Area under the curve of the first derivative from test start until MCF is reached

Courtesy of Klaus Görlinger, Tem Innovations, Munich, Germany

a lot of inappropriate prophylactic interventions with FFP or PCC can be avoided without increased incidence of bleeding complications [28, 106–116]. Furthermore, EXTEM and FIBTEM CT correlate well with plasma concentrations of DOAC measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (e.g., dabigatran (r = 0.92–0.99) and rivaroxaban (r = 0.83)) [24–27]. Here, ECATEM CT prolongation is highly specific for direct thrombin inhibitors such as dabigatran, argatroban, and bivalirudin (r = 0.85–0.99) [79–81].

The clot formation time (*CFT*) in seconds indicates the time between 2 and 20 mm clot firmness amplitude is achieved. The CFT corresponds to the kinetic time (k) of TEG™ assays and reflects the kinetic of clot formation. CFT mainly depends on thrombin generation, platelet count and platelet function, as well as fibrinogen concentration and fibrin polymerization and correlates well but nonlinearly with maximum clot firmness (r = 0.89) [31]. However, CFT can also be prolonged due to anticoagulants.

The alpha angle (α) in degree (°) reflects the kinetics of clot formation, too, and is defined as the angle between the baseline and a tangent to the clotting curve through the 2 mm point. Since the alpha angle reflects the combined contribution of fibrinogen and platelets to clot strength, it cannot really be used to discriminate between fibrinogen and platelet deficits [39]. The combination of EXTEM and FIBTEM clot firmness parameters (A5, A10, or MCF) is needed for accurate discrimination [13, 14, 23, 32, 33, 37, 38, 41].

Clot Propagation (Clot Firmness) Parameters

One of the most important ROTEM™ parameters is maximum clot firmness (*MCF*) in mm which corresponds to the maximum amplitude (MA) of TEG™ assays. MCF is defined as the maximum amplitude of clot firmness reached during test runtime. Usually it takes about 30 min after CT to achieve MCF. The clot firmness amplitude reflects the mechanical strength of the clot and mainly depends on platelet count and platelet function, fibrinogen concentration and fibrin polymerization, factor XIII activity, and colloids.

In order to speed up decision-making in severe bleeding, the amplitude of clot firmness 5 or 10 min after CT (*A5* or

A10, respectively) is increasingly being used. A20 is used during quality control measurements. A5 and A10 correlate very well with the MCF (Spearman's coefficient of 0.91–0.98) and allow for decision-making within 10 to 15 min after starting the test [6, 13, 31–33, 41]. EXTEM and INTEM A5, A10, and MCF correlate with platelet count (r = 0.61–0.89) and fibrinogen concentration (r = 0.61–0.82) [13, 32, 41, 54–60, 63, 64]. FIBTEM A5, A10, and MCF correlate well with plasma fibrinogen concentration (r = 0.69–0.88) and factor XIII activity (r = 0.60) [13, 32, 41, 54–60, 63–65, 117, 118]. However, this correlation can be modified by several factors as summarized in Table 6.4 (Table 6.4). Finally, the calculated parameters PLTEM A5, A10, and MCF (EXTEM A5 (A10, MCF) – FIBTEM A5 (A10, MCF)) correlate well with platelet count (r = 0.64–0.90) [13, 63, 64, 145]. Notably, clot firmness parameters are superior in predicting bleeding compared to platelet count [146–150]. Furthermore, low clot firmness values have been demonstrated to be associated with an increased risk of hyperfibrinolysis. An EXTEM A5 ≤35 mm can identify more than 90% of patients developing hyperfibrinolysis, finally [33]. This is in line with the threshold of EXTEM A5 ≤35 mm reported by Davenport et al. to identify trauma-induced coagulopathy on arrival in the emergency room [151].

Table 6.4 Modification of the correlation between plasma fibrinogen concentration assays and FIBTEM clot firmness parameters (A5, A10, MCF)

Modification of the correlation between plasma fibrinogen concentration assays and FIBTEM clot firmness parameters (A5, A10, MCF)	
Plasma fibrinogen concentration assays in g/L (fibrinogen concentration measurement)	FIBTEM clot firmness parameter (A5, A10, MCF) in mm (fibrin polymerization measurement)
Different *measurement platforms* (intraclass correlations coefficients (ICC) for fibrinogen between 0.37 and 0.66 and for PT between 0.19 and 0.80) [119]	Differences between ROTEM *delta* and ROTEM sigma (ROTEM sigma A5 correlates better to Clauss fibrinogen (r = 0.85) compared to ROTEM *delta* (r = 0.70)) [118]
Intra-laboratory and *inter-laboratory variability* (0.02–0.04 and 0.01–0.10, resp.) [119]	Intra-operator and *inter-operator variability* (FIBTEM MCF CV = 8.3% vs. 6.9%, resp.) [7]
–	*Technical improvements in* ROTEM *sigma*: new mixer and firmware improves early availability of cytochalasin D (in FIBTEM C)
–	*Reagent improvements in* ROTEM *sigma*: FIBTEM versus FIBTEM PLUS (improved FIBTEM formulation containing cytochalasin D + albumin + GPIIbIIIa receptor antagonist) in the newest FIBTEM C version [120–122]
No effect of *hematocrit* because fibrinogen concentration is assessed in plasma after blood centrifugation	Effect of *hematocrit:* correlation between FIBTEM MCF and plasma fibrinogen is higher at lower hematocrit (<25%; r = 0.88) than at higher hematocrit (>30%; r = 0.67) [123]; in cardiac surgery with CPB: preoperative (r = 0.68) and post-protamine (r = 0.72) [124]
PT-derived versus Clauss fibrinogen: *dysfibrinogenemia* affects Clauss fibrinogen and PT-derived fibrinogen, differently [125]	FIBTEM MCF has a high sensitivity toward detection of different *congenital fibrinogen disorders* [126]
Effect of *factor XIII deficiency*: although Clauss fibrinogen was normal (at factor XIII activity of 20 ± 6 IU/dL), coagulation in FIBTEM was impaired, which FXIII administration tended to correct [127]	Effect of *factor XIII deficiency*: FIBTEM MCF is positively correlated with factor XIII activity (cirrhosis, r = 0.60; cardiac surgery, r = 0.32–0.56) [65, 68]
Effect of *colloids (HES > gelatin > albumin)*: increased turbidity results in overestimation of fibrinogen concentration in photo-optical Clauss methods [128], pronounced effect in Clauss reagents calibrated for low fibrinogen concentrations [129, 130]	Effect of *colloids (HES > gelatin > albumin)*: impaired fibrin polymerization results in low FIBTEM MCF [128]
PT-derived versus Clauss fibrinogen: effect of *heparin*; neither Clauss fibrinogen nor PT-derived fibrinogen is valid in the setting of high concentrations of heparin (on CPB) [131]; Clauss fibrinogen is significantly lower during CPB than after protamine (mean difference 1.2 g/L (95% CI, 1.03–1.4 g/L) [14]	*FIBTEM S (SUR without heparin inhibitor) versus FIBTEM (liquid) and FIBTEM C (beads in cartridge) (with heparin inhibitor; 5 IU/mL)*; FIBTEM MCF (liquid reagent) on CPB versus Clauss fibrinogen post-CPB, r = 0.78 [15]; FIBTEM S MCF correlation to plasma fibrinogen: pre-reperfusion period (LTX), r = 0.789; post-reperfusion period, r = 0.170 (contraindication for single-use reagents (SUR) according to the ROTEM instructions for use (IFUs)) [132]
Effect of *direct thrombin inhibitors* (DTIs: dabigatran, argatroban, bivalirudin): underestimation of plasmatic fibrinogen concentration with high variability between different turbidimetric assays [133]	Effect of *direct thrombin inhibitors* (DTIs: dabigatran, argatroban, bivalirudin): FIBTEM MCF is reliable even under high DTI concentrations [134–136]
Prediction of major bleeding (progress) and management of transfusion in cardiovascular surgery, liver transplantation, trauma, and PPH: plasma fibrinogen concentration is inferior to FIBTEM to predict (progress of) bleeding and massive transfusion [41, 137–139] and to guide bleeding management and improve patient outcomes in these clinical settings [9, 140–145]	*Prediction of major bleeding* (progress) and management of transfusion in cardiovascular surgery, liver transplantation, trauma, and PPH: FIBTEM (A5, A10, MCF) is superior to plasma fibrinogen concentration to predict (progress of) bleeding and massive transfusion [41, 137–139] and to guide bleeding management and improve patient outcomes in these clinical settings [9, 140–145]; e.g., FIBTEM A5 adjusted OR (95% CI; *P-value*) to predict progression of total blood loss >2500 mL in PPH, 0.85 (0.77–0.95; *P = 0.002*), versus Clauss fibrinogen, 0.93 (0.49–1.74; *P = 0.813*) [138]

Courtesy of Klaus Görlinger, Essen, Germany

A5 amplitude of clot firmness 5 min after CT, *A10* amplitude of clot firmness 10 min after CT, *CPB* cardiopulmonary bypass, *CV* coefficient of variation, *DTI* direct thrombin inhibitor, *HES* hydroxyethyl starch, *MCF* maximum clot firmness, *OR* odds ratio, *PT* prothrombin time, *r* Spearman's correlation coefficient rho, *SUR* single-use reagent

Clot Lysis Parameters

The clot lysis parameters maximum lysis (*ML*) and the lysis indices 30, 45, and 60 (*LI30, LI45*, and *LI60*) provide information about the activity of fibrinolytic enzymes, fibrinolytic inhibitors, and factor XIII [72–74, 152–154]. ML detected during runtime is described as the reduction in clot firmness after MCF was achieved in percentage of MCF. LI30, LI45, and LI60 indicate the remaining clot firmness in percentage of MCF still present 30, 45, and 60 min after CT, respectively. Notably, lysis parameters in TEG™ are defined differently regarding the time of assessment. The TEG™ lysis parameters LY30 and LY60 indicate the amount of lysis in percentage of MA, 30 and 60 min after MA is achieved. Accordingly, LY30 in TEG™ corresponds more closely to LI60 in ROTEM™ regarding runtime. The ROTEM™ lysis onset time (*LOT*) in seconds is characterized by the time period from CT until 15% of clot lysis is achieved [155, 156]. Notably, the correlation between severity of fibrinolysis and patient outcomes seems to be setting-specific. Whereas in severe trauma fibrinolysis within 1 h runtime >7.7% in rTEG and >18% in EXTEM is associated with increased mortality, even 50% fibrinolysis during the anhepatic and graft reperfusion phase of liver transplantation is not [157–160]. Notably, FIBTEM is much more sensitive and specific for the detection of hyperfibrinolysis compared to kaolin-TEG, rapid-TEG, or EXTEM [69, 70].

On the other hand, fibrinolysis shutdown (<2% fibrinolysis within 1 h runtime) can be associated with increased mortality even in trauma [157–159, 161]. Notably, fibrinolysis shutdown seems to play a major role in the pathophysiology of myocardial infarction, thrombosis, sepsis, and DIC [83, 85, 162–165].

Limitations of Viscoelastic Testing

A major limitation of standard viscoelastic testing is its insensitivity to the effects of antiplatelet drugs (e.g., cyclooxygenase-1 (COX-1) inhibitors and ADP ($P2Y_{12}$) receptor inhibitors) [93, 166]. This limitation is caused by the generation of high amounts of thrombin in viscoelastic test systems which mask the effects of antiplatelet drugs by stimulating the platelets via the thrombin receptor pathway (protease-activated receptor (PAR) 1 and 4). Since thrombin is the strongest activator of platelets, the inhibition of other pathways (e.g., arachidonic acid or ADP pathway) does not affect viscoelastic test results in the presence of high amounts of thrombin.

Furthermore, standard ROTEM™ and TEG™ assays are not sensitive to von Willebrand disease since the system does not include a collagen surface and does not induce high sheer stress [167]. However, a modification of ROTEM™ assays including a preincubation of the blood sample with ristocetin showed some promising results to improve test performance in patients with von Willebrand disease [168].

As shown in some case reports, CT in EXTEM and INTEM can be prolonged in patients with antiphospholipid syndrome (lupus anticoagulant) without increased bleeding tendency [169, 170]. However, ROTEM data in patients with antiphospholipid syndrome are sparse.

Finally, viscoelastic testing cannot detect endotheliopathy directly since endothelial cells have been included in the test system for research, only [171]. Indirectly, endotheliopathy can be detected by the presence of hyperfibrinolysis and heparin-like effects (HLE). The HLE occurs due to a damage of the endothelial glycocalyx in severe trauma/shock, infection/sepsis, and cirrhosis/liver transplantation with a subsequent endogenous heparinization [88, 172, 173]. The combination of severe hyperfibrinolysis and HLE can result in a flat-line – in particular in TEG™. In case of a flat-line in ROTEM™, an APTEM should be performed since this is actually the only viscoelastic assay available, which blocks both – hyperfibrinolysis and a HLE – and therefore allows for assessing residual hemostasis under these conditions [174].

ROTEM™ *Platelet* Module

To overcome the platelet function limitations, ROTEM™ *delta* can be combined with the ROTEM™ *platelet* module, which is CE-marked in Europe since November 2013 [46, 175]. It provides two channels for whole blood impedance aggregometry in addition to the four viscoelastic channels of ROTEM™ *delta* (Fig. 6.1a, c–e). Arachidonic acid (*ARATEM*), adenosine diphosphate (*ADPTEM*), and thrombin receptor-activating peptide-6 (*TRAPTEM*) can be used as activators in ROTEM™ *platelet*. The corresponding reagents are designed as user-friendly lyophilized single-use reagents. The main parameters of ROTEM™ platelet are the area under the curve (AUC in Ohm x min), the amplitude at 6 min (A6 in Ohm), and the maximum slope (MS in Ohm/min). AUC is the clinically most important parameter and reflects the overall platelet aggregation (Fig. 6.1e).

Platelet function analysis is much more susceptible to pre-analytic factors such as the anticoagulant used (citrate, lithium heparin, or hirudin), the size of the blood sampling vial, transportation with a pneumatic system, and resting time of the blood sample before analysis [176–179]. Therefore, these pre-analytic factors have to be standardized and validated, and hospital-specific reference ranges and cut-off values for therapeutic interventions should be established.

Whole blood impedance aggregometry has been shown to detect the effect of COX-1 inhibitors and ADP receptor inhibitors, effectively, and to predict stent thrombosis/ischemic events and bleeding/platelet transfusion in interventional cardiology and cardiac surgery [45–48, 51, 93, 180–184]. Furthermore, the effects of drugs, such as desmopressin, tranexamic acid, and protamine, on platelet function can be assessed by whole blood impedance aggregometry [185–189]. Beyond drug monitoring, the effect of cardiopulmonary bypass, extracorporeal life support such as extracorporeal membrane oxygenation (ECMO) and ventricular assist device (VAD), liver transplantation, trauma, and sepsis can be assessed with whole blood impedance aggregometry [49, 50, 189–194].

Predictive Value of Thromboelastometry and Impedance Aggregometry

The positive predictive value of thromboelastometry and impedance aggregometry to predict bleeding in elective surgery is low (15–50%), but the negative predictive value is very high (80–97%) [50, 139, 195, 196]. Therefore, pathologic thromboelastometry or impedance aggregometry results do not mean that the patient has to bleed. This is not a surprise since hemostasis provides several compensatory mechanisms such as high factor VIII levels in patients with low levels of vitamin K-dependent coagulation factors due to cirrhosis and high fibrinogen levels in patients with thrombocytopenia. Accordingly, pathologic thromboelastometry or impedance aggregometry results should only be treated in the presence of clinically relevant bleeding requiring a hemostatic intervention (*Don't treat numbers!*). In contrast to patients scheduled for elective surgery, in patients with preexisting hemostatic disorders, such as liver cirrhosis, trauma, sepsis, or specific drug effects, thromboelastometry and impedance aggregometry provide a positive predictive value, too [41, 49, 139, 193, 194, 197–200].

However, it is rather the question "Why does this patient bleed?" than "Will this patient bleed?" which can be answered by thromboelastometry and impedance aggregometry in the perioperative setting. Accordingly, the main advantage of thromboelastometry and impedance aggregometry is to identify or exclude a specific hemostatic disorder as the reason for bleeding in a timely manner, and ROTEM™ algorithms have to be understood as "*not-to-do algorithms*" by step-by-step exclusion of different coagulopathic reasons for bleeding. If both thromboelastometry and impedance aggregometry show normal results, the probability of coagulopathic bleeding is very low (<5%), and the patient should be rechecked for surgical reasons for bleeding (Fig. 6.3).

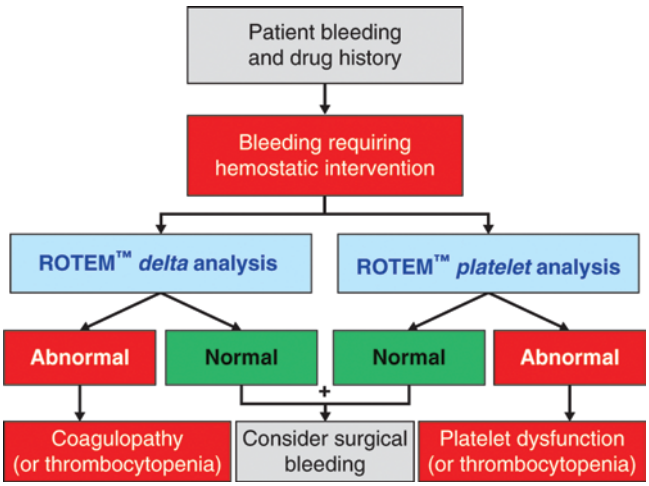


Fig. 6.3 ROTEM™ diagnostics flowchart (improved diagnostic performance by combining thromboelastometry (ROTEM™ *delta*) with whole blood impedance aggregometry (ROTEM™ *platelet*)) (Courtesy of Klaus Görlinger, Essen, Germany)

Prediction of Progress of Bleeding and (Massive) Transfusion

Plasma transfusion may improve outcome in patients requiring massive transfusion, whereas plasma transfusion in patients not requiring massive transfusion only shows an increase in complication rates, such as transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-related immunomodulation (TRIM), nosocomial infection, and sepsis [108, 116, 200–202]. However, prophylactic or inappropriate platelet transfusion might even be more harmful in several clinical settings [116, 203–208]. Thus, early prediction of massive transfusion is crucial for decision-making to start plasma transfusion in severe trauma, postpartum hemorrhage (PPH), and major surgery [138, 209, 210]. On the one hand, the need for massive transfusion can be predicted based on clinical scoring systems and, on the other hand, based on thromboelastometry (A5, A10, or MCF in INTEM, EXTEM, or FIBTEM) or impedance aggregometry results (AUC in TRAPTEM or ADPTEM) on arrival in the ER [41, 49, 151, 198, 211–213]. In these trauma studies, the optimum cut-off value to predict massive transfusion has been identified as EXTEM A5 ≤35 mm, INTEM A10 ≤44 mm, and FIBTEM A10 (MCF) ≤7 (9) mm [151, 198, 212]. None of the patients with a FIBTEM A10 ≥12 mm on admission received a massive transfusion finally [198]. EXTEM A5 (≤35 mm) was more accurate in predicting massive transfusion than INR (>1.2) [151]. These findings have been confirmed by an international prospective validation study in 808 trauma patients, identifying an optimum threshold for EXTEM A5 ≤40 mm and for FIBTEM A5 ≤9 mm (plasma fibrinogen

concentration ≤1.9 g/L) as a valid marker for TIC and predictor for massive transfusion [41]. Accordingly, the panel of the "2014 consensus conference on viscoelastic test-based transfusion guidelines for early trauma resuscitation" and the authors of the Lancet Neurology paper about the management of coagulopathy in traumatic brain injury recommend thresholds for EXTEM A5 (A10, MCF) <35 (45, 55) mm and for FIBTEM A5 (A10, MCF) <9 (10, 12) mm to consider platelet or fibrinogen administration in bleeding trauma patients, respectively [23, 214]. This is in line with the results of the prospective observational multicenter TACTIC trial, recommending a threshold of FIBTEM A5 <10 mm for fibrinogen replacement and a threshold of PLTEM A5 (EXTEM A5 – FIBTEM A5) <30 mm for platelet transfusion in bleeding trauma patients [215]. Chapman et al. could identify an optimum threshold for TRAPTEM of <53 Ohm x min (ROC AUC, 0.97) and for ADPTEM of <43 Ohm x min (ROC AUC, 0.95) in citrated blood samples at hospital admission for prediction of massive transfusion by impedance aggregometry using ROTEM™ platelet [49].

Similar cut-off values have been published to predict bleeding and transfusion in other perioperative settings. In postpartum hemorrhage (PPH), on multivariate analysis FIBTEM A5, but not plasma fibrinogen concentration, was independently associated with progression to bleeds >2500 mL and transfusion of at least 8 units of blood products [138]. Here, women with progression had a median (IQR) FIBTEM A5 and Clauss fibrinogen of 12 (7–17) mm and 210 (180–340) mg/dL, respectively, compared with 19 (17–23) mm and 390 (320–450) mg/dL for those not progressing. FIBTEM A5 was available about 10 min and Clauss fibrinogen about 65 min after venipuncture in this study. The higher fibrinogen requirements in PPH fits well with the increased reference ranges for FIBTEM and Clauss fibrinogen at the end of pregnancy [99–101, 103, 118]. A threshold of FIBTEM A5 <12 mm for fibrinogen replacement could also be confirmed by a randomized controlled trial assessing the effect of FIBTEM-guided fibrinogen concentrate administration versus placebo for treatment of postpartum hemorrhage as well as in an implementation study in Wales [145, 216, 217].

The best predictive value for bleeding in patients undergoing cardiac surgery with cardiopulmonary bypass has been identified as FIBTEM MCF <8 mm (plasma fibrinogen concentration <1.8 g/L) [137]. In patients preoperatively treated with thienopyridines (ADP receptor antagonists), the best cut-off value to predict bleeding for ADPtest (impedance aggregometry performed with Multiplate™, Roche Diagnostics, Mannheim, Germany) was 31 U (with a negative predictive value of 92% and a positive predictive value of 29%) [195]. If TRAPtest was ≥75 U, even ADPtest <22 U was not associated with severe bleeding (negative predictive value, 100%) [196]. A comparative study between the two impedance aggregometry devices Multiplate™ and the ROTEM™ *platelet* device identified the best cut-off value to predict bleeding at 5–10 min after heparin reversal with protamine as ASPItest ≤26 U, ARATEM ≤15 Ohm x min, ADPtest ≤33 U, ADPTEM ≤36 Ohm x min, TRAPtest ≤78 U, and TRAPTEM ≤78 Ohm x min. Transfusion requirements correlated significantly with the degree of inhibition and the number of platelet activation pathways inhibited [50]. This is in line with the results of other authors [195, 196].

In liver transplantation, the cut-off values that best predict bleeding and transfusion have been determined as EXTEM A10 (MCF) ≤35 (44) mm and FIBTEM A10 (MCF) ≤8 (9) mm [139, 197, 218].

Prediction of Thrombotic/Thromboembolic Events

Three important mechanisms are involved in the pathophysiology of DIC, microvascular thrombosis, and multiple organ failure: hypercoagulability, characterized by an increased clot firmness in EXTEM, INTEM (MCF >68 mm), and FIBTEM (MCF >22 mm); tissue factor (TF) expression on circulating monocytes and microparticles, characterized by a shortening of CT in NA-HEPTEM despite prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT); and fibrinolysis shutdown, characterized by less than 3% fibrinolysis within 1 h in NA-HEPTEM [73, 83–85, 104, 170]. This triad results in delocalization/dissemination of clot formation and microthrombosis and a simultaneous shutdown of the physiologic fibrinolytic cleaning system. Accordingly, it seems to be important to detect the time point when TIC shifts to DIC in trauma patients. This may also be one reason why tranexamic acid increased mortality in the CRASH-2 and WOMAN trial when given later than 3 h after injury [219–221] and why a fibrinolysis shutdown (here defined as LI60 >98% in EXTEM (<2% lysis in EXTEM within 60 min after CT) or LY30 <0.6% in rapid-TEG™ (<0.6% lysis within 30 min after MA)) detected in trauma patients at hospital admission was associated with increased mortality due to multiple organ failure [157–159].

By avoiding overtreatment and consecutive thrombotic/thromboembolic events, thromboelastometry is not only effective in stopping bleeding timely by guide therapy but is also a step forward to safer patient care [9, 140–145, 222–225].

Clot Firmness in EXTEM, INTEM, and FIBTEM

In a prospective observational study in 69 patients with cardiovascular diseases, Dimitrova-Karamfilova et al. assessed the ability of routine coagulation tests (PT, aPTT, fibrinogen, and platelet count) and ROTEM™ tests to identify patients with hypercoagulability and thrombotic complications [226]. No statistically significant difference could be found for routine coagulation tests. In contrast, significant difference in ROTEM™ parameters could be observed in the 35 patients with thrombotic complications compared to the 34 healthy controls. In particular, EXTEM and INTEM CFT and MCF were able to identify patients with thrombotic complications using a MCF cut-off value of >68 mm with a sensitivity and specificity of 94%. FIBTEM MCF, with a cut-off of >24 mm, achieved only a sensitivity and specificity of 77% and 88%, respectively. This suggests that an elevated fibrinogen level which compensates for a low platelet count seems not to increase the thrombotic risk. The EXTEM and INTEM thrombodynamic potential index (TPI = (100 × MCF/100 – MCF)/CFT), with a cut-off value of >3.5, provided even a sensitivity and specificity of 100% and 92%, respectively. In conclusion, ROTEM™ analysis was definitively superior to routine coagulation tests in identifying patients with thrombotic complications.

These results could be confirmed by another recently published prospective observational study in 318 noncardiac surgery patients. Hincker et al. evaluated preoperative routine coagulation tests (aPTT, INR, and platelet count) and ROTEM™ tests to identify patients at increased risk for postoperative thromboembolic complications [227]. Twenty-nine percent of the included patient population has been recruited from the orthopedic and spine department. Again, none of the routine coagulation tests has been useful in predicting thromboembolic events, but preoperative EXTEM and INTEM CFT, alpha angle, A10, and MCF were predictive for thromboembolic complications. INTEM and EXTEM A10 were the best predictors with a cut-off value of 61.5 mm and a ROC AUC of 0.75 and 0.72, respectively. None of the FIBTEM parameters predicted thromboembolic complications, confirming that elevated fibrinogen levels alone seem not to be an independent risk factor for thrombosis. However, increased FIBTEM MCF values (>19 mm) may play a role in non-cirrhotic and cirrhotic patients with portal vein thrombosis [170, 228–230] and in patients with increased flap loss rate (EXTEM MCF >72 mm and FIBTEM MCF >25 mm) in patients undergoing reconstructive microsurgery [231].

In obese patients, hypercoagulability (increased MCF in INTEM, EXTEM, and FIBTEM) and hyperaggregability (increased AUC in impedance aggregometry) can be detected, too. Here, hypercoagulability correlates with body mass index (BMI) and inflammatory markers [232].

Tissue Factor Expression on Monocytes, Microparticles, and Malignant Cells

Stimulation with bacterial toxins, activation of purinergic (ADP) receptors ($P2X_7$), stimulation by activated platelets, contact with surfaces of extracorporeal assist devices (e.g., cardiopulmonary bypass, ECMO, VAD, dialysis), and ischemia/reperfusion lead to tissue factor (TF) expression on circulating monocytes [73, 83–86, 104]. This TF expression in the intravascular space results in delocalization/dissemination of coagulation and is an early and important pathomechanism of DIC and thrombosis. Similar effects have been observed in patients with malignancies [229, 230, 233, 234]. TF expression on circulating cells can be detected very sensitively (in picomolar concentrations) but not specifically by a reduction in CT in NA-HEPTEM [83–86]. Since heparinoids (e.g., by glycocalyx degradation or therapeutic administration) can mask this effect, NA-HEPTEM – and not just NATEM – should be used in order to eliminate any interference by a potential heparin effect [83].

Notably, TF-expressing monocytes inhibit fibrinolysis through a thrombin-activatable fibrinolytic inhibitor (TAFI)-mediated mechanism, which is the next step to microthrombosis and multiple organ failure [235].

Hypofibrinolysis (Fibrinolysis Shutdown)

In contrast to TIC, physiologic fibrinolysis is shut down in the early phase of infection, sepsis, and thrombosis due to an upregulation of plasmin activator inhibitor type-1 (PAI-1) and activation of TAFI [85, 235–237]. Notably, whether the thrombin-thrombomodulin complex results in activation of protein C, with subsequent downregulation of PAI-1 and activation of fibrinolysis, or activation of TAFI – with subsequent shutdown of fibrinolysis – is regulated by platelet factor 4 (PF4) and dependent on the consumption of protein C as well as genetic polymorphisms [238, 239].

However, Chapman et al. could demonstrate that not only increased fibrinolysis but also a fibrinolysis shutdown at hospital admission is associated with increased mortality in trauma patients due to multiple organ failure [157–159]. Accordingly, Adamzik et al. showed that the ROTEM™ LI60 in NA-HEPTEM can discriminate between intensive care patients suffering from severe bacterial sepsis (NA-HEPTEM LI60 >96.5% corresponding to a ML <3.5% within 1 h after CT) and postoperative patients with just systemic inflammatory response syndrome (SIRS) or healthy volunteers [83]. Furthermore, the LI60 (ROC AUC, 0.901; $P < 0.001$) proved to be more accurate in detection of bacterial sepsis than classical laboratory parameters such as procalcitonin (ROC AUC, 0.75; $P < 0.001$). Interleukin-6 and C-reactive protein were not able to differentiate between sep-

tic and postoperative patients. The same research group also found that ROTEM™ findings were a better predictor of 30-day survival in septic patients than established risk scores (SAPS II, SOFA) [199].

In conclusion, both hyper- and hypofibrinolyis seem to play an important role in the pathophysiology of TIC and DIC, and viscoelastic testing may be helpful in differentiating between both pathophysiologic entities and right decision-making regarding the appropriate use and timing of antifibrinolytic therapy.

Prediction of Mortality

Viscoelastic testing has been shown to be a good predictor of mortality in trauma in a recently published systematic review of the literature [40, 217]. Levrat et al. included 87 trauma patients in a prospective observational trial. Patients with hyperfibrinolysis were more severely injured, had greater coagulation abnormalities, and had a higher mortality rate (100% vs. 11%) [240]. Schöchl et al. identified in their database 33 patients with hyperfibrinolysis at hospital admission retrospectively. They found hyperfibrinolysis to be a strong predictor for mortality (88%). Furthermore, it appeared that the earlier fibrinolysis could be detected by viscoelastic testing, the earlier the patient died, irrespective of appropriate treatment [241]. Theusinger et al. showed that in their patient population mortality in the trauma hyperfibrinolysis group (77%), as diagnosed by ROTEM™, was significantly higher than in the non-trauma hyperfibrinolysis group (41%) and the matched trauma non-hyperfibrinolytic group (33%). Accordingly, hyperfibrinolysis was significantly ($p = 0.017$) associated with increased mortality in trauma [242]. In contrast, even 50% fibrinolysis during liver transplantation is not associated with increased mortality [160].

In a prospective cohort study including 517 trauma patients, Rourke et al. found admission fibrinogen level to be an independent predictor of mortality at 24 h and 28 days. Hypofibrinogenemia could be detected early by FIBTEM A5 (A10), and administration of cryoprecipitate or fibrinogen concentrate could correct coagulopathy and improved survival [146]. Similar results were shown in a prospective cohort study in 334 blunt trauma patients performed by Tauber et al. They identified cut-off values of FIBTEM MCF <7 mm and EXTEM MCF <45 mm as predictors for increased mortality. EXTEM MCF was independently associated with early mortality, and hyperfibrinolysis increased fatality rates, too [212].

Furthermore, early platelet dysfunction after trauma and in sepsis is associated with increased mortality [49, 193, 194].

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