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Principles and Practice of Thromboelastography in Clinical Coagulation Management and Transfusion Practice

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In the recent years, thromboelastography has become a popular monitoring device for hemostasis and transfusion management in major surgery, trauma, and hemophilia. Thromboelastography is performed in whole blood and assesses the viscoelastic property of clot formation under low shear condition. Thromboelastography can be performed with a variety of activator and inhibitors at different concentrations representing the most important factors for different intervals and clot formation variables reported in multiple studies and algorithms. Furthermore, fibrinogen levels and platelet counts have a major influence on thromboelastographic variables. In addition, differences in patient populations, devices, and preanalytical conditions contribute to some conflicting findings in different studies.

ASIDE FROM CLOT formation, thromboelastography has been used to estimate thrombin generation, fibrinogen levels, platelet function, and clot dissolution by fibrinolysis, all of them with some limitations. Thromboelastography has been successfully used for patient coagulation assessment, hemostatic therapy and transfusion in trauma, perioperative care, and assessing bleeding in hemophilic patients. Thromboelastography-based algorithms reduce both transfusion requirements and blood loss in cardiac surgery, liver transplantation, and massive trauma. Because of different assay characteristics, the direct comparison of threshold values for hemostatic interventions or clinical outcomes is limited. The aim of this article is to review the working principles, the practical applications, and the interpretations of thromboelastography results. Based on current evidence, this review addresses the clinical utility and limitations of the thromboelastography in different clinical settings that frequently require blood product transfusion. This review should provide clinicians with the up-to-date information on proper interpretation and implementation of thromboelastography in transfusion practice.

Rapid assessments of hemostatic function and the prompt correction of coagulopathy are essential in the management of bleeding due to trauma, major surgery, or hereditary hemorrhagic conditions. The liberal transfusion of allogeneic blood products has been associated with adverse effects such as transfusion-transmitted infections, organ dysfunction, and increased mortality [1]. The beneficial effects of transfusion as to supporting oxygen-carrying capacity, intravascular volume, and improving hemostatic function may be thereby

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counterbalanced or at least questioned [2]. Screening for coagulation abnormalities and application of hemostatic interventions based on classical coagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) are of limited value in perioperative and acutely ill patients [3]. Whole blood testing by thromboelastography may offer advantages in these clinical settings. Originally invented in 1948 [4], its concept predates the introduction of the aPTT test in plasma [5]. Recent methodological improvements of thromboelastography have widely expanded its use from preclinical hemostasis research to point-of-care use in the emergency and the operation room. Two commercially available devices are TEG (Thromboelastograph; Haemoscope/Haemonetics, Niles, Ill) and ROTEM (Rotation Thromboelastometry; TEM International, Munich, Germany). The TEG system has been available for many years in the United States, whereas the ROTEM system has been recently approved by the Food and Drug Administration for clinical use. In this review, the term *thromboelastography* will be used to describe general principles of the common technology, but the differences between the 2 systems will be specified as TEG or ROTEM, respectively.

Technical and methodological aspects of thromboelastography have been recently discussed in detail [6-10], but practical aspects of its clinical applications have not been fully appreciated. In this article, we review the working principles, practical applications/interpretations, and limitations of TEG and/or ROTEM for the clinical use in the bleeding patient.

BASIC PRINCIPLES OF THROMBOELASTOGRAPHY

Thromboelastography is used to assess viscoelastic changes in clotting whole blood under low shear conditions after adding a specific coagulation activator. The viscoelastic (tensile) force between the cup and the immersed pin results from the interaction between activated platelet glycoprotein (GP) IIb/IIIa receptors and polymerizing fibrin during endogenous thrombin generation and fibrin degradation by fibrinolysis [11-15]. Thromboelastography had been used to assess hypo- and hypercoagulable states and to guide hemostatic therapies with fresh-frozen plasma, with platelet concentrates as well as with coagulation factor concentrates [14,16-18].

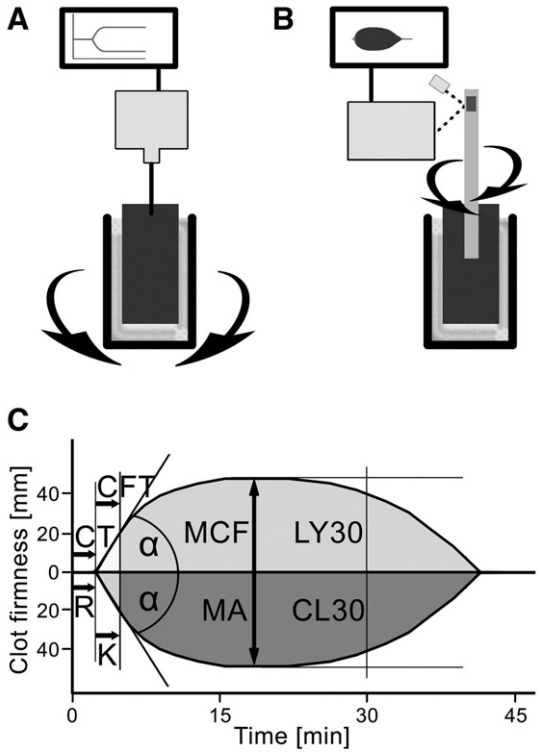

Fig 1. Working principle of TEG (panel A) and ROTEM (panel B). In TEG, the cup with the blood sample is rotating, whereas the torsion wire is fixed. In ROTEM, the cup is fixed, whereas the pin is rotating. Changes in torque are detected electromechanically in TEG and optically in ROTEM. The computer-processed signal is finally presented as a tracing. Panel C shows typical tracings from TEG (lower tracing) and ROTEM (upper tracing). For a detailed description of the terms used and the reference values of the various thromboelastographic parameters, see Tables 1 and 2.

In the original description [4], a metal pin suspended by a torsion wire is immersed in the nonanticoagulated whole blood in a metal cup. The modern systems closely follow this principle with some improvements and disposable parts. In case of TEG, the disposable cup moves back and forth through an arc of 4.75° around the fixed plastic pin (Fig 1A). In case of ROTEM measurements, the plastic pin rotates back and forth through an angle of 4.75° in the center of the plastic cup (Fig 1B). Once blood starts to clot, fibrin strands are formed, increasing the torque between the pin and the cup. Dissociation of fibrin strands from the cup wall (ie, clot retraction) or the degradation of fibrin by fibrinolysis decreases the torque [19]. The change of torque is detected electronically in TEG and optically in ROTEM. The computer-processed signal from either thromboelastography is presented as a tracing of clot formation and, if any,

clot dissolution (Fig 1C). The initial torque is assumed to be zero (no clot) for the signal processing; thus, it is important to start a measurement immediately after a coagulation trigger is added to the sample. Otherwise, a preclotted sample produces a false baseline when the pin is immersed into the sample blood.

Thromboelastography is commonly performed as a point-of-care coagulation test in the emergency and operation room. However, in some centers, the test is performed in specialized and centralized laboratories, permitting qualified personnel to perform this moderately complex coagulation test together with relevant quality control procedures. The availability of a rapid transport system for blood samples together with a computer network to provide online display of the analyses makes laboratory-conducted thromboelastography comparable with the bedside testing regarding the turnaround times and results [20].

Differences in Reference Ranges of TEG and ROTEM

Several comparative studies of TEG and ROTEM in clinical and laboratory settings demonstrated that the 2 systems are closely related but that their results are not completely interchangeable [9,10,21]. Some differences can be attributed to technical aspects of testing. The material surfaces of pin and cup can exert various extents of procoagulant activity. Therefore, data from older studies using TEG with metal cups and noncitrated (native) whole blood cannot be directly compared with more recent investigations using plastic cups and recalcified whole blood [6,22]. The reference values are also different among plasma and native or recalcified citrated blood [23,24]. However, the most important reason for different clot formation variables is the use of different activators at various concentrations [8,25]. Clinical reference values thus differ between the 2 systems and must be interpreted accordingly [10,26,27].

The use of citrated whole blood is the standard for thromboelastographic systems today. Before testing, citrated samples are recalcified by adding 20 μL of 0.2 mmol/L $CaCl_2$. It must be noted that blood sampling in sodium citrate tubes dilutes the blood samples by approximately 10%. In addition, citrate may affect platelet GPIIb/IIIa and therefore influence thromboelastographic measurements [23,28], which has to be considered in the interpretation of results [24], Such influences are limited when citrated plasma (without platelets) is used, for example, in hemostasis research [13,29], Therefore, the sample collection method needs to be standardized, and reference ranges for the specific method need be established.

Table 1. Terms Used for TEG and ROTEM

	TEG	ROTEM
Period to 2-mm amplitude	R time	CT
Period from 2 to 20 mm amplitude	K time	CFT
α Angle	α (slope between R and K)	α (angle of tangent at 2-mm amplitude)
Maximal strength	MA	MCF
Amplitude (at set time in min)	A30, A60	A5, A10, A15, A20, A30
Maximal lysis	–	ML
CL after 30 and 60 min	CL30, CL60	LY30, LY60
TTL	TTL (2-mm drop from MA)	LOT (85% of MCF)
Time to complete lysis	–	LT (10% of MCF)

Abbreviations: CT, coagulation time; CFT, clot formation time; MA, maximal amplitude; ML, maximal lysis; CL, clot lysis; TTL, time to lysis; LOT, lysis onset time; LT, lysis time.

Key Parameters and Reference Ranges

The main end point of TEG and ROTEM is the determination of viscoelasticity referred as amplitude and clot firmness, respectively (Fig 1C). The time course of viscoelastic changes is depicted as additional parameters to reflect the rate and stability of clot formation for clinical use (Table 1, Fig 1C).

Reference values for TEG are based on unspecified surgical patient samples of limited size (n = 41-178) [27]. References values for ROTEM were determined in a multicenter study in patients and healthy volunteers (n = 142-202) [26]. Reference ranges are shown in Table 2. It must be noted that normal values depend on preanalytical factors such as recalcification and time from blood sampling [26,28] and also on the type and final concentration of the activator [29,30]. The latter vary substantially between the 2 systems [8]. In particular, clotting time and clot formation time are strongly dependent on the type of activators used. Sorensen and Ingerslev [14] showed that the concentration of tissue factor relevantly influences thromboelastographic parameters [25].

Table 2. Reference Ranges of Different Thromboelastographic Parameters

	Test (activator)	R/CT (s)	K/CFT (s)	Angle α (°)	MA/MCF (mm)	ML (% of MA)
TEG	rapidTEG (tissue factor)	78-110	30-120	68-82	54-72	<15
	kaoTEG (kaolin)	180-480	60-180	55-78	51-69	<15
ROTEM	EXTEM (tissue factor)	35-80	35-160	63-81	53-72	<15
	INTEM (ellagic acid)	100-240	35-110	71-82	53-72	<15
	FIBTEM (tissue factor + cytochalasin-D)				9-25	<15

NOTE. Normal values are according to the manufacturer of ROTEM and TEG for citrated and recalcified blood samples.

The variation of test results is lower after extrinsic activation with tissue factor (coefficient of variation about 3%-5%) but substantially higher after intrinsic activation with kaolin or ellagic acid (coefficient of variation about 12%-15%). The variation is least for maximal amplitude/clot firmness (coefficient of variation about 5%), independent of the activator used [6].

In adult patients, normal values of maximal clot firmness (MCF) are positively correlated with increasing age, whereas clot formation time shortens in elderly patients [26]. This is most likely because of higher fibrinogen levels in older people [31]. Indeed, the strong interdependence of fibrinogen and thromboelastographic parameters has been shown in different studies [11,32,33]. There is also a small difference between sexes. Values of MCF were reported to be higher in women, probably because of lower hematocrit [26]. Anemia was found to relevantly increase MCF in ROTEM analyses that was attributed to a methodological issue rather than actual hypercoagulable state [34].

In neonates, coagulation time was reported to be reduced despite prolonged values of PT in 2 separate studies [35,36]. This may be attributed to lower antithrombin levels, which compensate for lower levels of coagulation factors [35,37,38]. In contrast, the influence of gestational age on MCF in neonates and children is less clear [35,36].

Available Coagulation Tests on TEG and ROTEM

Originally, celite was used as a contact activator on TEG, which was later replaced by kaolin (kaoTEG). A modification by addition of heparinase to neutralize the effects of heparin together with kaolin activation (hepTEG) was recently introduced to monitor underlying blood coagulability in the presence of heparin. Another modification is the so-called rapidTEG, where tissue factor is used as an activator in addition to kaolin [17,24,25]. RapidTEG is increasingly used, as it gives fast results on MCF, but its information on coagulation and clot formation time is very limited. Both kaoTEG and rapidTEG are insensitive to antiplatelet agents. PlateletMapping assay is used to evaluate the extent of platelet inhibition by aspirin or clopidogrel [39,40]. In this assay, thrombin generation in the sample blood is inhibited by adding heparin. Platelets are activated by adding a specific platelet activator (arachidonic acid for aspirin and adenosine-5′-diphosphate for clopidogrel), whereas fibrin polymerization is achieved by a mixture of reptilase (batroxobin) and activated factor XIII. The decrease in maximal amplitude

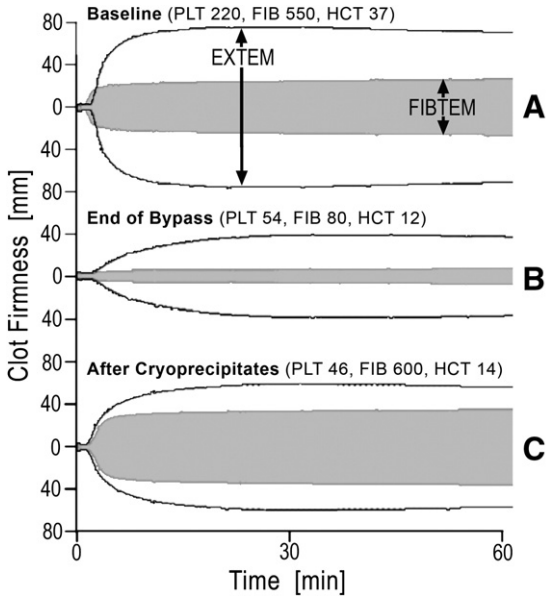

Fig 2. ROTEM tracings from a patient undergoing cardiac surgery at baseline (panel A) after severe dilution (panel B) during cardiopulmonary bypass and after substitution with cryoprecipitate (panel C). EXTEM and FIBTEM traces are overlaid. Platelet counts ($10^3/\mu L$), fibrinogen levels (milligram per deciliter), and hematocrit (percentage) are depicted for each time point. After substitution with cryoprecipitate, the EXTEM tracing normalizes because of the increase of fibrinogen levels (also evident in the FIBTEM tracing). Because of lower hematocrit, FIBTEM is much larger despite similar fibrinogen values at baseline and after cryoprecipitate substitution. PLT indicates platelet count; FIB, fibrinogen level; HCT, hematocrit.

relative to kaoTEG is used to calculate relative platelet inhibitions [40]. The PlateletMapping assay can be adapted on the ROTEM system [41].

Multiple liquid reagents are available for ROTEM [6]. A single-use reagent became recently available for all ROTEM tests for easier test performance with very good correlations to classical reagents [42]. EXTEM uses tissue factor as an activator of extrinsic pathway, whereas INTEM uses ellagic acid/phospholipids for contact activation. The HEPTEM test is a modified INTEM test that includes a heparin degrading enzyme. FIBTEM is used to estimate the extent of fibrin polymerization by inhibiting platelet function with cytochalasin-D after tissue factor activation (Fig 2) [43]. Systemic fibrinolysis can be diagnostically tested using the APTEM assay, in which aprotinin is added to inhibit plasmin [6,44]. Taken together, thromboelastography can be performed with a variety of activators and inhibitors. Each modification alters the assay's sensitivity and specificity. Although TEG and ROTEM share basic methodological principles, the 2 systems have different test characteristics that limit the direct comparison of measurements [10]. Therefore, threshold values for hemostatic interventions or clinical outcomes should be locally evaluated for each system and available hemostatic components.

COMPARISON OF THROMBOELASTOGRAPHY AND OTHER COAGULATION TESTS

PT/aPTT and Thromboelastography

For practicing clinicians, it is of interest to know whether the results of thromboelastography can be directly correlated with conventional coagulation tests. In particular, correlations between thromboelastographic coagulation time (Tables 1 and 2) and conventional PT and aPTT should be considered. In a recent clinical study of trauma-induced coagulopathy using ROTEM, the correlations between coagulation time in EXTEM/INTEM and PT/aPTT were rather poor (r = 0.47-0.53) [45]. Similarly, only weak correlations for R times in TEG with aPTT and PT have been described [24,46]. The lack of clear correlations can be partly explained by different preanalytical conditions, activators, and specimens (whole blood vs plasma). Nevertheless, some ROTEM parameters related to fibrin polymerization (eg, amplitude after 15 minutes, clot formation time) seem to be similarly useful for detecting coagulopathy as abnormal PT/aPTT values (>1.5 times normal) [45].

Thrombin Generation and Thromboelastography

In a small in vitro study with blood from 4 healthy volunteers, thrombin-antithrombin complex correlated well with total thrombus generation in thromboelastography [15]. Thrombin-antithrombin complexes reflect the amount of thrombin that is neutralized by antithrombin and serves as a surrogate marker for thrombin generation. On the other hand, total thrombus generation is calculated from the first derivative of the thromboelastographic waveform. The authors claimed that TEG can reasonably estimate thrombin generation by total thrombus generation [15]. Assuming normal platelet count, fibrinogen, and factor XIII levels, the rate of clot formation is proportional to the rate of thrombin generation. In hemophilic patients, thrombin generation is extremely small. Abnormal thrombus generation can be distinctively shown by the first derivative method in some but not all patients [25,47].

To increase thrombin generation, treatment with recombinant factor VIIa is often necessary in bleeding hemophilic patients with inhibitors against factor VIII. The off-label use of recombinant factor VIIa is also common in severe bleeding after cardiac surgery [48]. Coagulation monitoring with conventional tests (PT/aPTT) is not useful in dosing recombinant factor VIIa [49]. The use of thromboelastography seems to be advantageous in better approximating whole blood coagulation [3,50]. However, only a fraction (20-50 nM) of total thrombin generation is required to fully activate

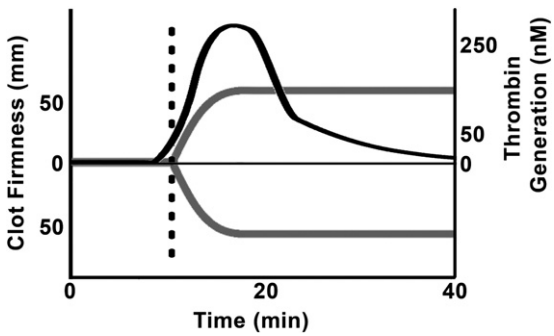

Fig 3. Typical traces of thromboelastography (the gray trace) and thrombin generation (the black trace). The dotted vertical line indicates where the conventional coagulation tests (PT/aPTT) stop in relation to thrombin generation and thromboelastography.

platelets, fibrinogen, and factor XIII [51], and the major part of thrombin generation takes place after fibrin polymerization (Fig 3) [52]. Therefore, procoagulant activity of factor VIIa was only visible when pretreatment thromboelastographic curves were significantly abnormal regardless of the bleeding status [47]. As an alternative, increased clot stability against fibrinolysis induced by tissue-type plasminogen activator in hemophilia models has been used as a surrogate marker of improved thrombin generation in thromboelastography [53,54].

The efficacy of recombinant factor VIIa to generate thrombin depends on available tissue factor [55]. Tissue factor concentrations in the standard EXTEM test are too high for delineating coagulation abnormality in hemophilia [6,56]. The use of diluted tissue factor (eg, Innovin 1:17000 resulting in tissue factor concentration of about 135 ng/mL) is advocated [14,25,50], but the clinical utility of diluted tissue factor in monitoring factor VIIa therapy is questionable based on the recent multicenter study [47]. Using kaolin as a contact activator may allow detecting hemostatic defects in hemophilic patients more reliably [57,58]. In fact, kaoTEG was also useful in sequential dosing of FEIBA (factor VIII bypassing activity) and factor VIIa in hemophilia A patients with severe recurrent bleeding [59].

In perioperative patients, fibrinogen and platelet counts are rapidly changing. Therefore, changes in the first derivative of the thromboelastographic waveform are more likely because of hypofibrinogenemia [11] or thrombocytopenia [29] rather than the decrease in thrombin generation [11,60]. The estimation of thrombin generation by thromboelastography has many limitations, and a fluorogenic measurement of thrombin generation is preferable [61].

Platelet Function and Thromboelastography

Platelets exert important hemostatic functions in vivo including primary plug formation (adhesion/aggregation) and providing a catalytic surface for serine protease (eg, thrombin) activation. Thromboelastography is useful for evaluating the overall interaction between platelet GPIIb/IIIa receptors and fibrinogen [62], as activated platelets provide ample binding sites (GPIIb/IIIa) for fibrinogen. A correlation between platelet count and maximal amplitude in TEG had been described as early as 30 years ago [22,63], which has been reconfirmed in recent studies that used the ROTEM system [26,29]. Platelet count also influences clotting time, clot formation time, and α angle in thromboelastographic tests [29,64]. The minimal platelet count for "normal" clot formation is not known, and it is markedly influenced by the fibrinogen level [26]. The α angle and MCF are greatly decreased when platelet count falls below 50 000/μL [65,66].

Inhibitory effects of antiplatelet agents can be assessed by the PlateletMapping assay as described above. However, platelet adhesion activity under high shear (>1500 per second) cannot be evaluated on thromboelastography because of its low shear state (0.1 per second). Other diagnostic systems such as PFA-100 or platelet function analyzers should be used for the diagnosis of von Willebrand disease and platelet dysfunction related to a deficiency of GPIbα receptors [67].

Plasma Fibrinogen and Thromboelastography

Plasma fibrinogen concentration is often determined by a turbidometric (Clauss) method that depends on thrombin-induced fibrin formation. This method is affected by multiple factors including the presence of colloid solutions (eg, hetastarches, gelatines) [68,69] and direct thrombin inhibitors (particularly bivalirudin) [70].

For TEG, the functional fibrinogen assay is available for estimated fibrinogen level [27], but published data are scarce. Alternatively, a mixture of reptilase and activated factor XIII has been used in TEG to determine fibrinogen levels in whole blood [71], but adding exogenous factor XIII may limit assessments of impaired fibrin polymerization because of decreased factor XIII after hemodilution. FIBTEM test has been commonly used on ROTEM for clinical assessment of plasma fibrinogen. In this test, cytochalasin-D is added to EXTEM activation so that platelet cytoskeletal reorganization, and thus, GPIIb/IIIa interactions with fibrinogen are inhibited [43,62].

The MCF on FIBTEM test is correlated with plasma fibrinogen levels [45]. In trauma-induced coagulopathy, a FIBTEM amplitude after 10 minutes (A10) of less than 5 mm was reported to be a good predictor of low plasma fibrinogen (<100 mg/dL) with a sensitivity of 91% and a specificity of 85% [45]. It is suggested that hetastarches and gelatines lower clot firmness of FIBTEM much more than crystalloids [43,68].

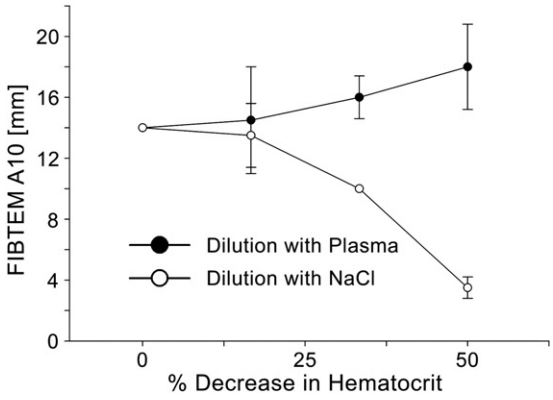

Fig 4. The FIBTEM amplitude depends not only on the fibrinogen level but also on the hematocrit. The graphs shown are derived from an in vitro study in whole blood from 4 healthy patients (unpublished data). The FIBTEM amplitude after 15 minutes decreases with increasing dilution with saline (NaCl) because of decreasing fibrinogen levels but increases when the whole blood is diluted with autologous plasma (fibrinogen levels remain unchanged). The latter finding is explained by decreased hematocrit.

In clinical studies with dilutional or trauma-induced coagulopathy, the implementation of thromboelastography led to an increased use of fibrinogen concentrate and cryoprecipitate [16,72]. Thromboelastography has been used to monitor the effect of fibrinogen therapy because clot firmness as well as other clot formation parameters responds well to increased fibrinogen levels [11,32,57]. FIBTEM clot firmness can be affected by factors other than fibrinogen, for example, factor XIII [73], hematocrit [71] (Fig 4), and potentially platelet count [12]. The latter is particularly noticeable in thrombocythemia (ie, incomplete platelet inhibition) when TEG assay is used with abciximab [12].

FIBRINOLYSIS AND THROMBOELASTOGRAPHY

In the presence of systemic fibrinolysis (eg, release or use of tissue plasminogen activator [tPA]), the thromboelastographic amplitude may rapidly decrease after maximal amplitude (compare traces in Fig 5A and C). When the decrease of the amplitude over 1 hour is more than 15% of maximal amplitude, hyperfibrinolysis is suspected. Using the ROTEM system, a specific assay containing aprotinin (APTEM test) might confirm the presence of hyperfibrinolysis [6]. The release of tPA from endothelial cells is stimulated under conditions of inflammation and stress [74], and hyperfibrinolytic tracings may be observed in major trauma, liver transplantation, and cardiac surgery [6,44,75]. Because plasma normally contains high concentrations of plasminogen activator inhibitor 1 and α_2-antiplasmin, the fibrinolytic response is generally limited to the local milieu (ie, surface of thrombus) [3]. The absence of hyperfibrinolysis on thromboelastography does not exclude localized fibrinolysis, but it suggests that the systemic concentration of tPA is not high enough to induce ex vivo hyperfibrinolysis. In agreement, the fibrin clot is more susceptible to fibrinolysis after massive hemodilution because of progressive loss of endogenous fibrinolysis inhibitors [60]. In trauma patients, overt hyperfibrinolysis is evident on thromboelastography in 15% to 20% of patients [44,75,76]. The recently published CRASH-2 trial suggests that there is ongoing fibrinolysis in trauma patients because a small but statistically significant benefit from early administration of an antifibrinolytic agent was observed [77]. Indeed, fibrinolysis seems to be an integral part of trauma coagulopathy

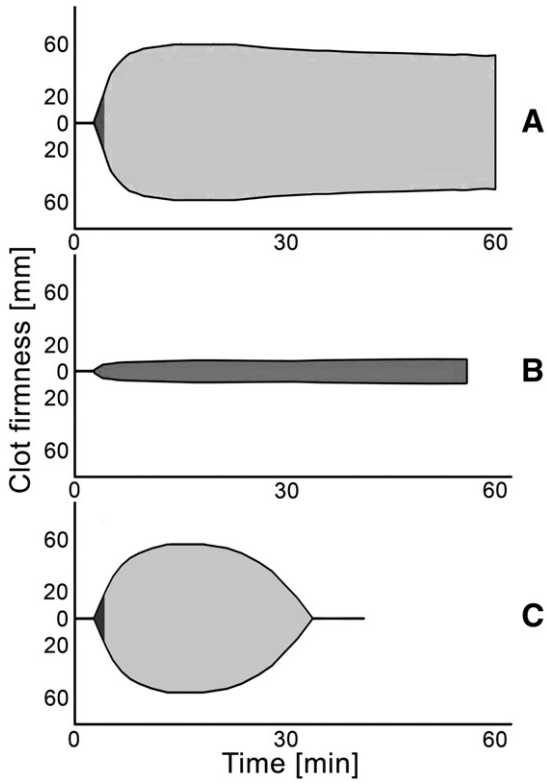

Fig 5. Typical EXTEM (panels A and C) and FIBTEM (panel B) traces in undiluted whole blood showing clot retraction (panel A) and hyperfibrinolysis (panel C). Panel A shows no fibrinolysis, but clot retraction is evident by the missing fibrinolysis in the FIBTEM test (panel B). Panel C shows hyperfibrinolysis after in vitro addition of tPA.

[76], which is associated with severity of injuries and leading to increased mortality [44,76,78], especially in case of the early onset of hyperfibrinolysis in thromboelastography [44].

It is important to differentiate between hyperfibrinolysis and clot retraction [19]. Clot retraction is a small decrease (<15%) in amplitude after the maximal amplitude/clot firmness (Fig 5A). It is most likely due to the dissociation of fibrin strands from the cup wall when the interaction of fibrin and platelets GPIIb/IIIa receptors is intense. Clot retraction is thus more apparent in the presence of higher platelet counts [19,79], whereas it is hardly seen after platelet inhibition (Fig 5B) or hemodilution. Finally, in vitro studies suggest that decreased FXIII concentrations might be associated with increased fibrinolysis on ROTEM [73,80], but this hypothesis was not supported by a recent clinical evaluation of ROTEM traces and FXIII levels in neurosurgical patients [81].

EFFECTS OF HEMATOCRIT ON THROMBOELASTOGRAPHY

In the flowing (arterial) blood, platelets are preferentially distributed near the vessel wall (margination) because of the red cell mass [82]. The platelet count measured in a static blood sample does not reflect in vivo platelet concentration by the injured vessel wall, and this may explain a relatively low incidence of spontaneous bleeding until the platelet count is below 10 000/μL [83]. In addition, the red blood cells facilitate platelet aggregation by releasing adenosine diphosphate under shear flow [84]. In contrast to in vivo conditions, thromboelastography is performed under low shear (0.1 per second), and the red cell mass entrapped in the fibrin network may interfere with the spreading of fibrin strands [71] or with the interaction of fibrin and platelets GPIIb/IIIa [79]. Indeed, α angle and MCF values are increased by approximately 5° and 10 mm, respectively, in anemic patients (mean hematocrit, 28%) compared with healthy subjects (mean hematocrit, 41%) [34]. In agreement, increasing hematocrit decreased clot strength in a TEG assay to determine fibrinogen after addition of reptilase and FXIIIa [71]. Direct effects of low hematocrit (anemia) rather than an imbalance between thrombin and antithrombin may also explain the findings of "hypercoagulable state" in TEG traces after hemodilution to hematocrits of 10% to 30% [85-87].

Taken together, low hematocrit most likely worsens bleeding in vivo [88] but improves thromboelastographic variables in vitro. Thromboelastographic results should be carefully interpreted along with severity of anemia, hemodilution, and other clinical findings (eg, microvascular bleeds), especially in patients after trauma or major surgical procedures.

HYPERCOAGULABILITY AND THROMBOELASTOGRAPHY

Thromboelastography is substantially influenced by the platelet count [29], platelet-fibrin interaction, and fibrin polymerization [11,62]. Enhanced clot formation on thromboelastography may be associated with a hypercoagulable state. Indeed, maximal clot amplitude and coagulation index, derived from an equation including *R* time, K time, maximal amplitude, and angle α [89], were found to be higher in surgical patients with thrombotic events than in healthy controls [90]. However, the accuracy of thromboelastography in predicting thrombotic events including deep vein thrombosis, vascular graft occlusion, ischemic stroke, and myocardial infarction is highly variable [90]. A recently published systematic review found an association of hypercoagulable traces in thromboelastography with thrombotic events after major surgery in some but not all studies [90]. Elevated platelet counts and high fibrinogen levels are encountered frequently in the postoperative period, resulting in high maximal clot amplitude/firmness [91]. In contrast, in heparin-induced thrombocytopenia, the risk of thrombotic events is very high, although low platelet count results in normal or even reduced clot amplitude/firmness [92].

Similar to conventional PT/aPTT tests, diagnosing hypercoagulable states (eg, deficiency of antithrombin or protein C) by thromboelastography is more difficult than detecting hypocoagulability because of supraphysiological procoagulant stimuli used in testing. In particular, hypercoagulable state can be related to the faulty systems shutting down activated coagulation factors such as thrombin, factor Va, and factor Xa. The inhibitions of these factors take place after the formation of activated platelets and fibrin, so most clot-based tests are not sufficiently sensitive to detect hypercoagulable state. Therefore, thromboelastography should be

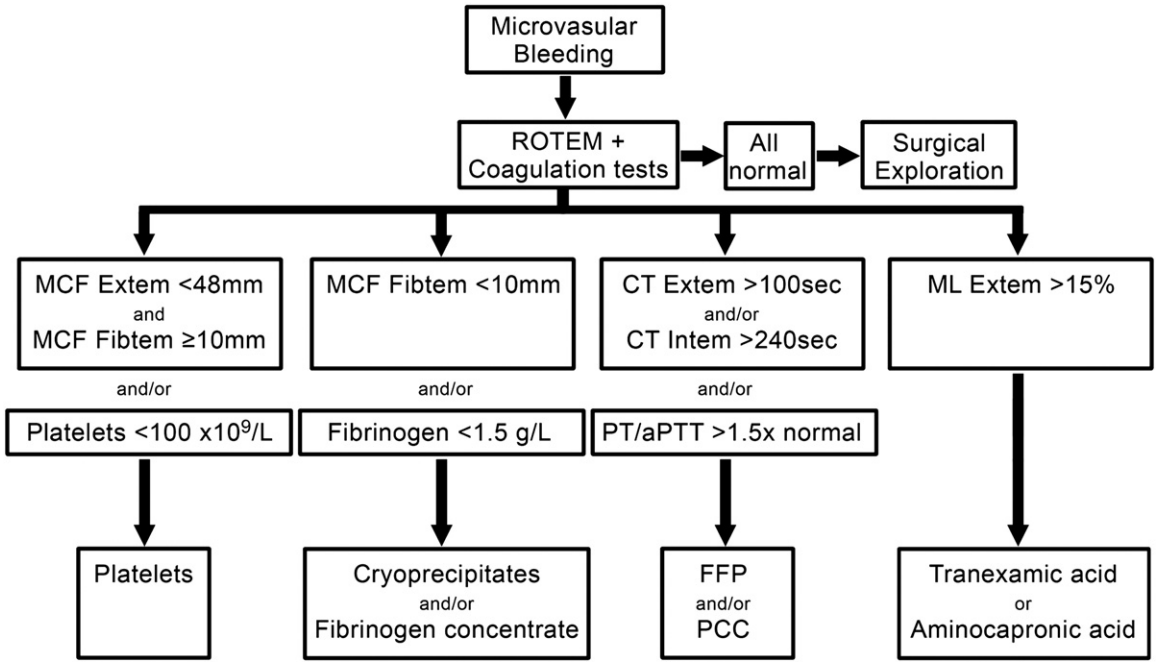

Fig 6. A proposed transfusion algorithm in bleeding patients based on conventional coagulation and ROTEM parameters. For an explanation of the abbreviations of the ROTEM parameters, please refer to Table 1.

used primarily to detect thrombocythemia or hyperfibrinogenemia, and other specific assays should be considered to confirm hypercoagulable states. The latter assays include the assessment of antithrombin activity, protein C or protein S activity, and activated protein C–modified aPTT (for factor V Leiden) [93]. The calibrated automated thrombin generation assay (with diluted tissue factor) can be useful in the evaluation of hypercoagulable state as it delineates the overall balance of procoagulant and anticoagulant factors [37,94,95].

CLINICAL ALGORITHMS FOR BLEEDING MANAGEMENT

Thromboelastography-guided transfusion algorithms have successfully been implemented in the treatment of bleeding patients after major surgery [16,24,72,96,97]. An example of a transfusion algorithm based on ROTEM is shown in Figure 6. It must be clearly stated that this algorithm has not yet been validated. In general, EXTEM and FIBTEM are used primarily to evaluate overall clot stability and fibrin polymerization, respectively (Fig 2). Thromboelastography-based cutoff values are not well validated and, therefore, arbitrary. Importantly, cutoff values should be individually used and adapted based on the available coagulation tests and therapeutic options. Clinical presence or likelihood of bleeding should be considered in a specific patient population before implementing therapies according to laboratory results. Serial measurements of thromboelastography can be used to guide hemostatic interventions in conjunction with other clinical and laboratory parameters including body temperature, pH status, hematocrit, platelet count, and PT/aPTT. Goal-orientated coagulation therapy based on thromboelastographic findings and preset transfusion algorithms [16,24,97,98] may be advantageous to so-called damage control resuscitation with a fixed ratio administration of blood products [99,100]. The key concept of damage control resuscitation is a preemptive transfusion of fresh-frozen plasma and platelet concentrates to prevent the development of a coagulopathy. A substantial number of patients, however, may receive too many hemostatic products or inappropriate ones, putting these patients at risk for adverse effects of transfusions including acute lung injury, inflammation, infections, and increased mortality [1,101]. Finally, normal findings in thromboelastography may permit a prompt reexploration of surgical causes of bleeding.

The use of transfusion algorithms in conjunction with thromboelastography has been shown to reduce

both transfusion requirements and blood loss in cardiac surgery, liver transplantation, and trauma care [16,21,72,97,98]. It must be noted that the implementation of a simple transfusion algorithm without coagulation testing can also reduce transfusion requirements [102,103]. A recent meta-analysis failed to show a relevant influence of thromboelastography on major morbidity and mortality in bleeding patients [104]. However, this meta-analysis is limited by the heterogeneity and the low number of included studies. Further large studies investigating the potential benefits of thromboelastography-guided algorithms are thus warranted.

CONCLUSION

Thromboelastography seems to be valuable for a rapid assessment of hemostatic clot stability, providing reliable and clinically valuable information on coagulation processes, and implementing goal-directed transfusion therapy in bleeding patients in major surgery and trauma and, with some limitations, in bleeding hemophilic patients. Perioperatively, physicians might therefore use thromboelastography as a unique window into complex coagulopathy. As with other laboratory tests, these in vitro methods cannot detect the in vivo contribution of endothelial cells or shear forces of blood flow on local clot formation and fibrinolysis. Thromboelastography is particularly sensitive to changes in fibrin polymerization and platelet count. Therefore, it is most useful for early detection of trauma and surgery-related dilutional coagulopathy in which plasma fibrinogen and platelets fall rapidly [105]. In addition, it is valuable in guiding the use of cryoprecipitate or purified fibrinogen concentrate [106] and potentially platelet transfusion. Using thromboelastography in goal-orientated algorithms, clinicians may be able to optimize targeted transfusion therapies with specific coagulation factor(s) instead of empirically administering multiple components with potentially hazardous effects [101]. Understanding the working principles and limitations of thromboelastography is thereby critical to interpret test results and establish hemostasis safely and efficaciously. However, large controlled clinical trials comparing strategies of coagulation management and establishing algorithms and thromboelastographic cutoff values for transfusion of blood product components are needed.

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