Thromboelastometry guided therapy of severe bleeding

Essener Runde algorithm

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Keywords

Coagulopathy, haemorrhage, thromboelastometry, ROTEM

Summary

Both, severe haemorrhage and blood transfusion are associated with increased morbidity and mortality. Therefore, it is of particular importance to stop perioperative bleeding as fast and as possible to avoid unnecessary transfusion. Viscoelastic test (ROTEM® or TEG®) allow for early prediction of massive transfusion and goal-directed therapy with specific haemostatic drugs, coagulation factor concentrates, and blood products. Growing consensus points out, that plasma-based coagulation screening tests like aPTT and PT are inappropriate for monitoring coagulopathy or guide transfusion therapy. Increasing evidence of more than 5000 surgical or trauma patients points towards the beneficial effects of a thrombelastography or –metry based approach in diagnosis and goal-directed therapy of perioperative massive haemorrhage. The Essener Runde task force is a group of clinicians of various specialties (anaesthesiology, intensive care, haemostaseology, haematology, internal medicine, transfusion medicine, surgery) interested in perioperative coagulation management. The ROTEM diagnostic algorithm of the Essener Runde task force was created to standardise and simplify the interpretation of ROTEM® results in perioperative settings and to present their possible implications for therapeutic interventions in severe bleeding. To exemplify, this text mainly focuses on coagulation management in trauma.

Schlüsselwörter

Koagulopathie, Massivblutung, Thromboelastometrie, ROTEM

Zusammenfassung

Sowohl massive Blutungen wie auch Blut-(produkt)transfusionen sind mit einer Zunahme der Morbidität und Mortalität verbunden. Es ist daher von entscheidender Bedeutung, perioperative Blutungen schnellstmöglich zu stoppen und somit unnötige Transfusionen zu vermeiden. Viskoelastische Tests (ROTEM® oder TEG®) ermöglichen eine frühzeitige Erkennung einer drohenden Massivtransfusion sowie die zielgerichtete Therapie mit spezifischen, die Hämostase fördernden Medikamenten, Gerinnungsfaktorkonzentraten und Blutprodukten. In zunehmender Einigkeit werden plasma-basierte Gerinnungstest wie aPTT und PT als ungeeignet zur Diagnostik einer Koagulopathie oder Steuerung der Transfusionstherapie angesehen. An mittlerweile über 5000 operativen und traumatischen Patienten konnte der sinnvolle Einsatz thrombelastometrischer und -grafischer Verfahren zur Diagnose und zielgerichteten Therapie massiver Blutungen gezeigt werden. Die „Essener Runde" ist eine Gruppe aus klinisch tätigen Medizinern verschiedener Disziplinen, die sich mit perioperativer Gerinnung beschäftigt. Der diagnostische ROTEM-Algorithmus der Essener Runde wurde entwickelt um eine Standardisierung und Vereinfachung der Interpretation von ROTEM® Ergebnissen im perioperativen Umfeld zu ermöglichen und die sich daraus ergebenen therapeutischen Optionen zu beschreiben. Der Text zeigt dies am Beispiel des Gerinnungsmanagements bei Polytraumata.

Risks of blood transfusion

Both, severe haemorrhage and blood transfusion, are associated with increased morbidity and mortality (58).

In addition to the high incidence of inappropriate blood transfusion documented by the SHOT report (86), further transfusion-related adverse events have to be considered such as

- nosocomial infections and sepsis due to transfusion-related immunomodulation (TRIM) or
- bacterial contamination (the latter especially by platelet concentrates),

- thromboembolic complications (i. e., stroke, myocardial infarction) and
- acute lung injury (ALI).

ALI is caused (29) either by
- antibodies directed toward human neutrophil antigens in fresh frozen plasma (FFP) or platelets (TRALI = transfusion-related acute lung injury) or,
- volume congestion (TACO = transfusion associated circulatory overload) – more often but less dramatically.

Although there is no rapid test for TRALI and it is difficult to differentiate between TRALI and other causes of ALI, the 2006 SHOT report noticed:

> TRALI is the most important cause of transfusion-associated morbidity and mortality (86).

Although preferring male donor plasma might reduce the incidence of TRALI (13), the 2010 SHOT report still recommends robust systems to prevent issues due to the transfusion of FFP from female donors or pooled platelet concentrates suspended in female donor plasma (58).

A significant association between FFP transfusion and various infectious complications in critically ill surgical patients was found (78). A multicentre, prospective cohort study including 1175 patients with blunt trauma and subsequent haemorrhagic shock reported that FFP was independently associated with a 2.1% and 2.5% increased incidence of multiple organ failure and ARDS for each transfused unit, respectively (95).

> Therefore, it is of particular importance to stop perioperative bleeding as fast and as possible to avoid unnecessary transfusion.

Shortcomings of conventional coagulation tests

Yet, standard plasmatic coagulation screening tests such as activated partial thromboplastin time (aPTT) or prothrombin time (PT) are weak predictors of bleeding in the critically ill patients (15) and suboptimal for monitoring coagulopathy or guide hae-

mostatic therapy (51, 59). The poor correlation between these routine coagulation tests and clinical bleeding in trauma and major surgery may be explained by the new cell-based model of haemostasis (47).

Furthermore, the turn-around time of conventional coagulation tests performed in the central laboratory is 45–90 min (34, 41, 95). This time-lag is too long to use these results for a targeted haemostatic therapy.

> By thromboelastometry as a point-of-care (POC) test the turn-around time can be reduced to 15–25 minutes, enabling a timely and targeted coagulation therapy (41).

This article presents a basic algorithm for interpretation of thromboelastometry results and provides recommendations for targeted treatment of severe bleeding.

Transfusion strategies in severe bleeding

At presence, three strategies towards therapy of haemorrhage do exist:
- a ratio-based concept currently favouring a ratio 1:1:1 of packed red blood cells (PRBC) : FFP : platelets (PLT). This approach is called "damage control resuscitation" or "damage control haematology".
- an individualised, lab-based concept based on INR, aPTT, platelet count and other conventional laboratory tests,
- an individualised, goal-directed, near-patient concept based on POC testing analysing coagulation and platelets' function with viscoelastic and aggregometric tests such as
  - thromboelastometry / thrombelastography (ROTEM/ TEG) and
  - whole blood impedance aggregometry (Multiplate).

The third strategy is the requisite for a therapeutic intervention with specific coagulation factor concentrates ("theranostic" approach). This concept is increasingly accepted and may replace "damage control resuscitation" as soon as the devices and drugs become available in quantity and comprehensively (68).

Most cohort studies dealing with transfusion protocols based on transfusion packages (e. g., five units of PRBC + five units of FFP + five single donor or one pooled platelet concentrate) are of retrospective design and have a survival bias (46).
- On the one hand, early administration of FFP is essential to avoid dilutional coagulopathy in a FFP-based haemostatic concept (31).
- On the other hand, FFP transfusion in patients who do not achieve the level of massive transfusion is associated with an increased incidence of sepsis, acute lung injury and multiple organ failure (7). In particular this applies to patients receiving AB0-compatible but not AB0-identical FFP transfusion in order to start therapy early with pre-thawed FFP before patients' blood group is known.

However, it is common consensus that FFP transfusion in non-massively transfused patients is inappropriate and should be stopped as soon as possible or even better avoided (77, 87).

Advantages of viscoelastic tests

Viscoelastic tests (ROTEM or TEG) allow for early prediction of massive transfusion and goal-directed therapy with specific haemostatic drugs, coagulation factor concentrates, and blood products (70, 83). In several cohort studies, this POC-based management was associated with
- reduced transfusion requirements,
- reduced incidence of transfusion-associated adverse events, and
- improved patients' outcomes (69, 83).

These results could be confirmed recently by a prospective randomised clinical trial in coagulopathic cardiac surgical patients demonstrating a significant reduction in transfusion requirements, transfusion-associated adverse events, and costs, as well as improved outcomes including six-month mortality in the POC compared to the control group (97).

In principal, these concepts should be integrated in a hospital adapted guideline / standard operating procedure (SOP), as multiple publications show an association between implementation of a massive bleeding protocol and improved patients' outcome (16, 18, 20).

Essener Runde task force

Essener Runde task force is a group of clinicians interested in perioperative co-agulation management and working in various specialties:

- anaesthesiology,
- intensive care,
- haemostaseology,
- haematology,
- internal medicine,
- transfusion medicine,
- surgery.

Essener Runde was founded in 2001 to ex-change experience and discuss diagnostic and therapeutic options in the manage-ment of perioperative haemostasis. Since then, the group meets 3–4 times a year. In particular, the group is interested in point-of-care testing with viscoelastic methods such as thromboelastometry, as it is a func-tional assay which provides clinically rel-evant information, i. e., whole blood clot strength, enabling evaluation of both, plas-matic and cellular components of clot formation, within 15–20 minutes (51).

Principles of viscoelastic tests

In 1948, Hartert was the first to monitor whole-blood coagulation using thromb-elastography by measuring shear elastic modulus (dyne per cm^2) during clot formation (43). Providing a graphic pres-entation of the fibrin polymerisation and its lysis, he recorded the viscoelastic changes occurring during coagulation. Re-ferring on this principle, today two POC devices can be used: the

- classical thromblelastography (TEG, Haemonetics, Braintree, MA, USA) and
- thromboelastometry (ROTEM, Tem In-ternational GmbH, Munich, Germany).
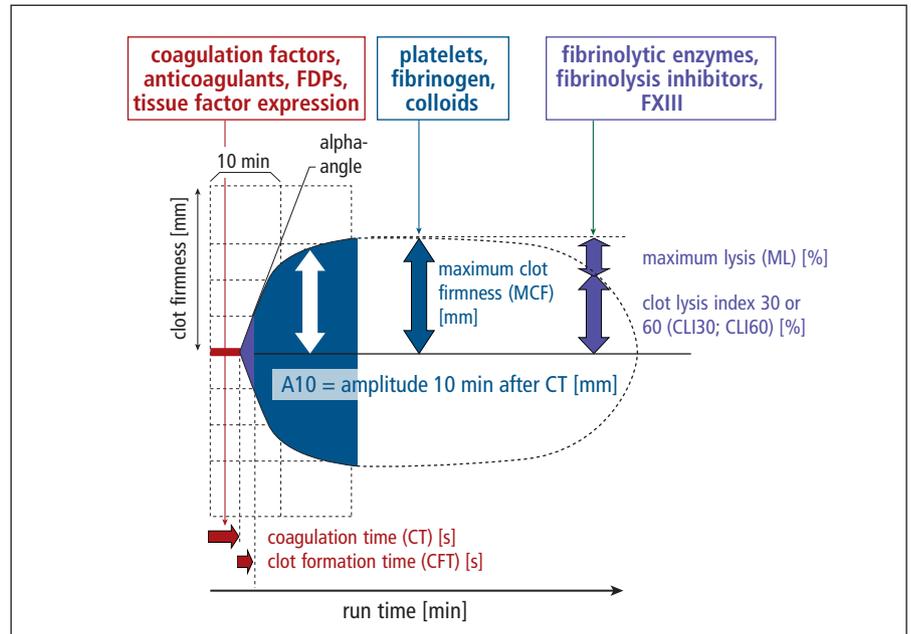
Fig. 1   ROTEM-tracing, parameters and influences: every square is 10 min on the horizontal axis. α-angle: slope of tangent at 20 mm amplitude; CT (coagulation time): time until start of clot formation (detection of a clot firmness of 2 mm); CFT (clot formation time): increasing polymerisation of fibrin and beginning interaction between fibin(-ogen) and platelets (time between detection of a clot firmness of 2 and 20 mm); MCF (maximum clot firmness): interaction between fibin(-ogen) and platelets; CLI (clot lysis index): physiological lysis within 60 min < 15% of MCF

Usually, citrated blood samples are used, so as to perform measurements immediately at the bedside in the operation room or at the intensive care units as well as in the central laboratory within two hours (51). A pin is suspended within a blood-filled cup. The pin is connected to a torsion wire (TEG) or the movement of the pin is recorded contactless by an optical device to assess the viscoelastic changes during co-agulation (ROTEM). In the ROTEM sys-tem, the pin is stabilised by a ball-bearing in order to avoid artefacts due to shock and agitation. This enables its mobile use as a real point-of-care device. The movement is initiated from either the cup (TEG) or the pin (ROTEM). The forming of fibrin be-tween the cup and the pin causes an in-creased (TEG) or reduced (ROTEM) movement of the pin by measuring mech-anical impedance, which is detected and displayed as a graph on a computer screen.

This text focuses on the interpretation of ROTEM results. Citrated whole blood (300 µl) is re-calcified with 20 µl of $CaCl_2$ 0.2 mol/l (STARTEM). The tool enables to

perform four tests simultaneously. Coagu-lation can be activated with tissue factor (EXTEM) or ellagic acid (INTEM) in order to speed up analysis and standardise the in vitro process. Additionally, reagents can be added to analyse

- EXTEM with
  - inhibition of fibrinolysis (by adding aprotinin, APTEM) or
  - inhibition of platelet function (by adding cytochalasin D, FIBTEM) and
- INTEM with neutralisation of heparin effects (by adding heparinase, HEPTEM).

An automated program navigates and standardises pipetting. Using liquid reagents, all extrinsically activated tests in-clude a heparin inhibitor, which eliminates heparin effects up to a heparin concen-tration of 5 IU per ml blood.

Current understanding of haemostasis as proposed by Hoffman's cell-based model (47) is displayed by the initial phase of the tracing:

Tab. 1   Reference ranges of ROTEM parameters: This algorithm displays a simplified schematic diagram. Therefore, it cannot represent all possible clinical settings and does not replace the individual clinical decision.

	coagulation time CT [s]	clot formation time CFT [s]	amplitude after CT [mm]		maximum clot firmness MCF* [mm]	clot lysis index [%]	
			10 min A10	20 min A20		30 min CLI30	60 min CLI60
INTEM	100–240	30–110	44–66	50–71	50–72	94–100	85–100
EXTEM	38–79	34–159	43–65	50–71	50–72	94–100	85–100
HEPTEM	100–240**	30–110			50–72		
FIBTEM			7–23	8–24	9–25***		
APTEM	38–79	34–159			50–72		

*usually available after 20–40 min; **A markedly reduced CT in HEPTEM compared to INTEM indicates a heparin effect.
***MCF < 9 mm indicates reduced fibrinogen plasma concentration (<100 mg/dl) or fibrin polymerization disorders. MCF > 25 mm increased fibrinogen plasma concentration (≥300 mg/dl). Therefore, analyses possibly show normal MCF in INTEM and EXTEM despite thrombocytopenia.

> Coagulation time (CT in ROTEM) / r-time (TEG) and clot formation time (CFT in ROTEM) / k-time (TEG) relate to the initiation phase and the amplification phase, respectively (56).

Main thrombin generation is reflected by the alpha-angle, clot strength by the maximum clot firmness (MCF in ROTEM) / maximum amplitude (MA in TEG) and clot stability by maximum lysis (ML) or clot lysis index (CLI) (72). ROTEM tracing is shown (►Fig. 1), and the parameters' normal ranges (►Tab. 1). The ROTEM system has been CE marked, ISO certified, and FDA approved showing that it has passed validation for performance evaluation and verified to be adequate for its intended use (25). ROTEM thromboelastometry yields consistent values between centres and provides general orientating reference ranges (60). Timing is essential. Shortening of the turn-around time by ROTEM analysis compared to conventional laboratory testing has been demonstrated by Haas et al. recently (41). A10 values (clot firmness 10 minutes after CT) are able to predict MCF within 10 minutes (coefficient of determination [r^2] of >0.9 between A10 and MCF) (21, 35, 38). However, the complete tracing of a thromboelastometry/-graphy takes up to 60 minutes if late hyperfibrinolysis should be detected or excluded since hyperfibrinolysis is defined as a decrease of the maximum amplitude by more than 15% within one hour (5).

A modification of the TEG using tissue factor and kaolin as activators is called rapid-TEG (r-TEG). These results are also available within 15–25 minutes and can be used to predict the need for early blood transfusion, too (17, 49). Furthermore, Theusinger et al. demonstrated the reproducibility of ROTEM results over time (up to 120 min) in 48 patients and 10 healthy volunteers (91).

Essener-Runde algorithm

The ROTEM diagnostic algorithm of the Essener Runde task force (►Fig. 2) was created to standardise and simplify the interpretation of ROTEM results in perioperative settings and to present their possible implications for therapeutic interventions in severe bleeding. It was primarily developed as a basic diagnostic tool and has been specified later for specific clinical settings such as trauma, liver transplantation, and cardiac surgery at the University Hospital Essen (33, 36, 39, 81). In all these clinical settings transfusion requirements as well as the incidence of massive transfusion decreased significantly after implementation of these POC-algorithms (35–37, 39, 40, 97). Several centres in Austria (Innsbruck and Salzburg) as well as in Germany (Essen, Cologne and Cologne-Merheim) use similar POC-algorithms with comparable reduction in transfusion requirements in different clinical settings (39, 40, 69, 81, 82). To exemplify, this text mainly focuses on coagulation management in trauma. However, the basic diagnostic algorithm is used in the setting of

liver transplantation and cardiac surgery, too.

As stated before, ROTEM should be an integrated part of the hospital's massive bleeding protocol (16, 18, 20). It should be mentioned, however, that implementation of SOPs and algorithms per se improves patient outcome. Of note, ROTEM-guide therapy with haemostatic drugs and coagulation factor concentrates should only be initiated in the presence of diffuse bleeding. Surgical bleeding has to be treated adequately.

Interpretation of ROTEM results
EXTEM, FIBTEM, APTEM

- If EXTEM's CT is prolonged, a deficiency of the vitamin K-dependent factors II, VII, IX and/or X can be assumed.
- If EXTEM's (or INTEM's) A10 (or MCF) is reduced or CFT prolonged, a fibrinogen deficiency or fibrin polymerisation disorder (FIBTEM: A10 is reduced, too) or a low platelet count or severe platelet dysfunction (FIBTEM: A10 is normal) is most likely the cause of bleeding. Both can be differentiated by A10 (or MCF) in FIBTEM, as described.
- If EXTEM's (or INTEM's) CLI is reduced, fibrinolysis is present at a CLI < 85% within 60 min. Fulminant fibrinolysis is defined as CLI > 50% within 30 min.
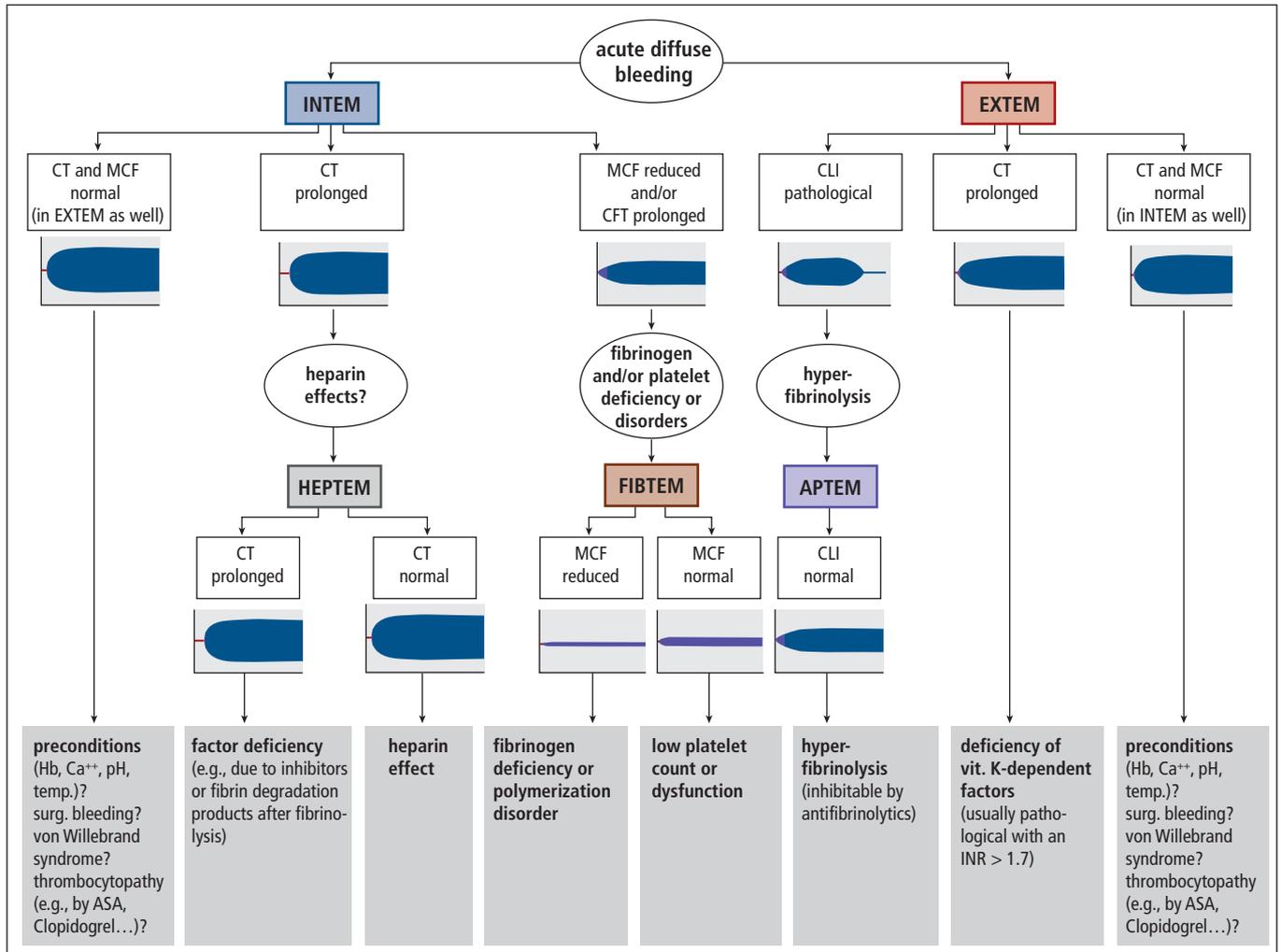- APTEM assesses whether an antifibrinolytic drug is effective to stop lysis. If

Fig. 2   ROTEM diagnostic algorithm of the „Essener-Runde" task force

CLI in APTEM remains pathological this may be due to platelet-mediated clot retraction or reduced cross-linking of fibrin monomers due to a deficiency of FXIII (33, 98).

INTEM and HEPTEM

If INTEM's CT is prolonged, HEPTEM can be used to differentiate between a

- heparin effect (HEPTEM: CT is normal) and
- deficiency of coagulation factors (HEPTEM: CT is prolonged, too).

Therefore, in bleeding patients with a normal CT in HEPTEM but prolonged CT in INTEM a heparin effect has to be assumed. This can be due to heparin infusion/injection (e. g., therapeutic heparinisation, anti-

coagulation during haemodialysis and other extracorporeal systems, heparin-block of large bore catheters), use of a cell saver system in an emergency modus with low washing volume (in any kind of massive bleeding), insufficient dosage of protamine for heparin-reversal, heparin redistribution after CPB, or liberation of heparinoids after reperfusion of the liver graft during liver transplantation.

On the other hand, a prolongation of CT in INTEM and HEPTEM, in combination with a normal CT in EXTEM, indicates a deficiency of one or more of the coagulation factors of the intrinsic pathway VIII, IX, XI or XII.

- However, factor XII deficiency is not associated with bleeding.
- Factor IX deficiency would have been balanced by previous PCC adminis-

tration (indicated if CT in EXTEM is prolonged, too).
- Isolated factor XI deficiency is rarely associated with low thrombin generation and severe bleeding even if the activity of FXI is below 10% (23).
- Factor VIII activity usually is elevated in patients with liver cirrhosis (93). Furthermore, factor VIII activity increases early in severe trauma or major surgery but may drop down later during severe bleeding and massive transfusion (89). Therefore, administration of a factor VIII concentrate or FFP may be considered in ongoing bleeding under these conditions (33).

In case of combined deficiency of coagulation factors of the intrinsic pathway and a heparin effect, both, CT in INTEM and
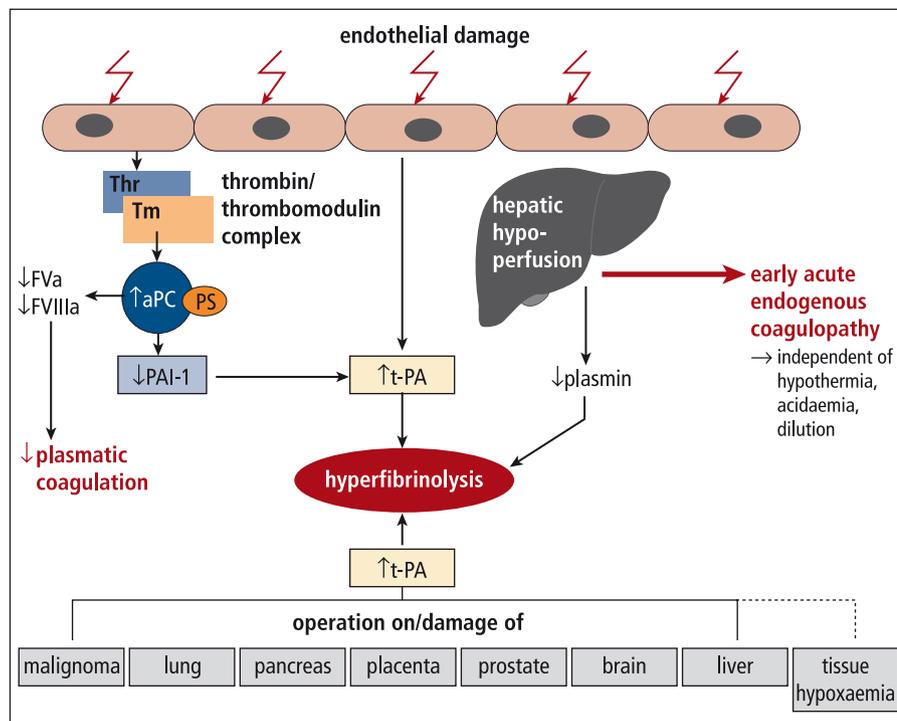
Fig. 3 Hypoxaemia by hypoperfusion causes increased endothelial expression of thrombomodulin (Tm). The complex of thrombin (Thr) and Tm activates protein C, which – amplified by protein S (PS) – inactivates the accelerators FVa and FVIIIa and thereby decreasing plasmatic coagulation. Furthermore, large amounts of activated protein C (aPC) inactivate plasminogen activator inhibitor (PAI), the most essential antagonist for tissue plasminogen activator (t-PA). Together with increased plasmin levels, hyperfibrinolysis is triggered. Increased levels of t-PA are also induced by traumatic or surgical damage of tissue from lung, pancreas, placenta, prostate, brain, or liver; modified (8, 9, 53).

HEPTEM, are prolonged but CT in INTEM is longer than CT in HEPTEM.

Limitations

If INTEM and EXTEM show regular CT and MCF, the following limitations of ROTEM analysis should be considered. Impaired in-vivo haemostasis due to disturbed preconditions of haemostasis (Hb, Ca_i^{++}, pH, core temperature) cannot be detected if ROTEM analysis is performed at 37°C (65). Although ROTEM analysis can be performed at patient's temperature (between 30 and 40°C), usually it is performed at 37°C since detection or exclusion of a coagulation factor deficiency is aimed by assessing CT in EXTEM and INTEM. A coagulopathy based on hypothermia, acidosis or hypocalcaemia can be assumed based on measuring patients' core temperature and blood gas analysis. Furthermore, impaired primary haemostasis due to von Willebrand's disease or antiplatelet drugs (e.g.,

induced by acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor, cangrelor, or low-dose abciximab, eptifibatide, or tirofiban) cannot be detected by ROTEM analysis.

The same is true for thrombocytopathy. Platelet aggregation induced by thrombin generated in ROTEM analysis will overlay a potential drug-induced platelet dysfunction (5).

Trauma-induced coagulopathy
Pathophysiology

The current understanding of the pathology of trauma-induced coagulopathy (TIC) focuses on the importance of (hyper-)fibrinolysis (8, 9). While an internationally accepted name is still missing, the "acute coagulopathy induced by trauma and shock (ACoTS)" is a discrete disease which has decisive influence on survival (64).

Hyperfibrinolysis is clinically characterised by non-surgical, diffuse bleeding from mucosal or damaged tissue, new bleeding from vesical or gastric tubes or puncture sites.

Furthermore, it has to be considered that fibrinogen is the first procoagulant factor to decrease below critical and substitution demanding levels in severe haemorrhage (45). Of note, the similarities of tissue injury after trauma and surgery (63) are focusing on the severity of tissue damage / hypoperfusion and not on its origin (28, 54, 88) (▶Fig. 3). While there are many reasons for depletion of fibrinogen in trauma (75), severe fibrinogen deficiency in a bleeding patient should alert to fibrinolysis (79).

Primary fibrinolysis is an integral part in the pathogenesis of ACoTS (55). ROTEM is a fast and reliable method to detect perioperative fibrinolysis (62). ROTEM-based diagnosis of fibrinolysis is predictive for patients' outcome (79) since significant differences in mortality were detected for defined ROTEM thresholds (50, 88). Of course, only systemic hyperfibrinolysis can be detected by viscoelastic tests. Therefore, treatment with antifibrinolytic drugs may be effective to reduce transfusion requirements even in patients without any sign of hyperfibrinolysis in ROTEM or TEG.

In principle, in vivo effects of shear stress or endothelial cells cannot be detected by an in vitro laboratory method (5). However, ROTEM analysis timely detects systemic changes of coagulation with a sensitivity and specificity between 75% and 100%, especially in TIC (62, 84). An abnormal MCF measured by thromboelastometry on admission reliably predicts the need for massive transfusion (19, 61). The use of ROTEM or TEG for monitoring of perioperative haemostasis is advocated by the American Society of Anaesthesiologists (1), the 2nd edition of the European trauma guideline (74) and the German S3-guideline on trauma (2).

Tab. 2
Summary of ROTEM-based therapeutic options in massive haemorrhage; modified (2, 64)

step		therapy
1.	stabilization of concomitant factors (prophylaxis and therapy)	• core temperature ≥ 34°C • pH ≥7.2 • ionised Ca^{++} ≥ 0.9 mmol/l
2.	substitution of oxygen carriers	**PRBC** (functionally: Hb 6[-8] g/dl, but haemostatically in active severe bleeding: Hct ≥ 30% or Hb ~ 10 g/dl [6.2 mmol/l]), resp.
3.	inhibition of potential (hyper)fibrinolysis (always before fibrinogen!)	**tranexamic acid** initial 2 g (25 mg/kg bw) for expected or proven hyperfibrinolysis: ML_{EXTEM} >15% anytime within 60 min
4.	substitution of coagulation factors (for ongoing, severe bleeding)	if **FFP,** then ≥ 30 ml/kg bw if CT_{EXTEM} < 80 s **and** CT_{HEPTEM} > 280 s (despite application of PCC and prior normalized $A10_{EXTEM}$ and $A10_{FIBTEM}$) **and fibrinogen** (2-)4(-6) g if $A10_{EXTEM}$ < 45 mm **and** $A10_{FIBTEM}$ < 15 mm **and PCC** initially 25 U/kg bw if CT_{EXTEM} > 80 s if necessary 1–2× **FXIII** 1250 U (15–20 U/kg bw) if $CLI60_{EXTEM}$ > 12% **and** $CLI60_{APTEM}$ > 10% **and** $CLI60_{XIII}$ < 10%
	and (suspecting thrombocytopathy) enhanced platelet adhesion + endothelial release of VWF and FVIII	**DDAVP (= desmopressin)** 0.3 µg/kg bw over 30 min if AUC-ASPI < 200 or AUC-ADP < 300 AU × min (Multiplate®)
5.	substitution of platelets for primary haemostasis	**platelets** if $A10_{EXTEM}$ < 45 mm **and** $A10_{FIBTEM}$ > 15 mm
6.	if necessity of a thrombin burst	**rFVIIa** initially 90 µg/kg bw on a case-by-case basis, if other therapeutic options fail, after consideration and correction of concomitant factors (if CT_{EXTEM} < 80 s **and** $A10_{EXTEM}$ > 50 mm **and** $A10_{FIBTEM}$ > 18 mm **and** Multiplate® ok **and** no surgical bleeding)
	for ongoing, severe bleeding	no antithrombin substitution

> Using point-of-care devices to detect and treat coagulation disturbances in severely bleeding patients should always be an integrated part of "damage control resuscitation" (3, 24).

Until major bleeding has been stopped, a mean arterial pressure of about 65 mmHg should be targeted (74) in patients without central nervous system damage. This should be done by restrictive volume therapy guided by repetitive measurements of lactate and base deficit (94). The German Medical Association emphasises plasma should not be applied as primary volume substitution and in case of coagulation factor and inhibitor deficiencies that can be treated more effectively and with better tolerance by using coagulation factor concentrates (grade of recommendation "1C+" which is a strong recommendation, valid for most patients, and fits the keyword "shall") (4, 10).

While choosing different fluids for volume therapy (crystalloids vs. colloids, HES vs. gelatine), different effects on haemostasis have to be considered; see for example (44, 67). The discussion concerning the optimal fluid for volume resuscitation in severe haemorrhage remains controversial (11). Initially, fluid therapy may start with crystalloids (2, 74). If the patient becomes haemodynamically instable, colloidal solutions may be indicated (74), possibly HES 130/0.4 (2) or gelatine. Haemodilution by both, crystalloids and colloids, will impair coagulation (6). Aiming at normothermia, patients' core temperature should remain >34°C (65) by using solely warmed infusions (3). Every volume therapy should be done only via a warming device with a fluid temperature of 40–42°C (92). Lactacidosis will impair pH and base deficit until restoration of sufficient tissue perfusion. As the activity of enzymatic coagulation factors are pH-dependent, buffering may be recommended only prior to the application of drugs affecting thrombin generation (2, 64). Lastly, depending on the severity of the haemorrhage, the replacement therapy should be made in a stepwise approach.

A small, retrospective matched-pair analysis of trauma cohorts, including 18 patients in each group, comparing FFP-based therapy without ROTEM analysis vs. ROTEM-based administration of coagulation factor concentrates without FFP transfusion reported significant differences with regard to the need for allogenic blood transfusion and the incidence of multiple organ failure. This may provide a signal supporting the ROTEM-based management of acute post-traumatic coagulopathy with coagulation factor concentrates rather than with traditional FFP transfusions (69). Furthermore, a goal-directed and ROTEM-based management of traumatic coagulopathy was successful not only in restoring haemostasis but also in minimising requirements for transfusion of allogenic blood products (80). Essener Runde developed a ROTEM-based table of therapeutic interventions (▶ Tab. 2) by adapting the progressive options published in the

• updated European trauma guidelines "*We suggest that thromboelastometry also be performed to assist in characterising the coagulopathy and in guiding haemostatic therapy (Grade 2C)*." (74),

Tab. 3 Fibrinogen dosage (32, 71) calculated for normovolaemia and Hb of about 10 g/dl; with hypervolaemia, Hb < 10 g/dl, and severe bleeding the increase may be reduced. No sufficient data exists for body weight < 20 kg or > 80 kg

body weight (bw)	targeted increase in plasma fibrinogen concentration in g/l <u>or</u> targeted increase in FIBTEM's A10 (MCF) in mm, resp.			
	0.5 g/l or 4 mm	1.0 g/l or 8 mm	1.5 g/l or 12 mm	2.0 g/l or 16 mm
20 kg	0.5	1	1.5	2
40 kg	1	2	3	4
60 kg	1.5	3	4.5	6
80 kg	2	4	6	8
x kg	**25 mg/kg bw**	**50 ml/kg bw**	**75 mg/kg bw**	**100 mg/kg bw**
fibrinogen dose (g) =	**targeted Δ plasma fibrinogen concentration (g/l) × body weigt (kg) / 20**			

- German S3-guideline on trauma "*Thrombelastography or –metry may be performed to guide coagulation diagnosis and substitution. GoR 0*" (2),
- the journal *Intensive Care Medicine* (64).

Like most other published algorithms, this one has not yet been validated in a prospective randomised trial, too.

Therapeutic principles of TIC and severe haemorrhage

1. The stabilisation of preconditions of haemostasis (body temperature, pH, ionised calcium) (65) is the first prophylactic **and** therapeutic action.
2. Affected haemostasis appears long before impaired oxygenation (42). While increasing evidence points to a detrimental effect of red blood cell transfusion on general patient survival (30), in severely bleeding coagulopathic patients restrictive transfusion triggers may be unfavourable (66).
3. The results of the double-blind, randomised, multicentre and multinational CRASH-2 trial showed promising effects of an early antifibrinolytic therapy with tranexamic acid (TxA) within the first 3 hours after trauma and the lack of additional vascular occlusive effects (84). Even in an expected fibrinolysis it is sufficient to give 1–2 g of TxA (corresponding to 12.5–25 mg per kg body weight) (26). However, administration of TxA later than three hours after trauma was associated with increased mortality (85), and therefore, should be restricted to patients with detected hyperfibrinolysis.

4. Still, the application of FFP remains the cornerstone of coagulation therapy for many clinicians. This point of view should be challenged. The coagulation factors V, XI and VWF:CP (aka ADAMTS13) are the only factors that can be replaced solely by FFP and not by coagulation factor concentrates (10). The sole indication for FFP with at least moderate evidence (73) is massive transfusion. To gain increasing coagulation factor activities in ongoing haemorrhage, a patient needs at least 30 ml FFP per kg body weight (15, 26). However, FFP may cause serious side effects (29, 86). Systematic use of ROTEM may enable a complete abandonment of FFP (40, 69, 82). Compared to fixed ratio transfusion concepts (e.g., 1:1:1), ROTEM-guided haemostatic algorithms based on first-line therapy with fibrinogen and prothrombin complex concentrates (PCC) significantly reduced exposure of trauma patients as well as patients undergoing liver transplantation or cardiac surgery to allogenic blood products (36, 37, 83, 97). Of course, abandonment of FFP might result in increased crystalloid and colloid infusion. However, our approach targets at stopping bleeding as soon as possible,

thereby reducing overall volume requirements.

5. A plasma fibrinogen concentration below 2 g/l has been shown to be associated with increased bleeding in several clinical settings, e.g., neurosurgery, postpartum haemorrhage, cardiac surgery, and scoliosis surgery (12, 14, 52). ROTEM-guided goal-directed therapy with fibrinogen concentrate and PCC was associated with a significant decrease in transfusion requirements, the incidence of massive transfusion and the incidence of thromboembolic events in cardiac surgery (36, 97). Furthermore, the transfusion requirement for PRBC (2 (0–4) vs. 8.6 (4–11) units) and the incidence of pulmonary embolism (1.1 vs. 4%) in patients undergoing liver transplantation is lower at University Hospital Essen using a coagulation management algorithm based on first-line therapy with coagulation factor concentrates guided by ROTEM compared to another recognised liver transplant centre using a coagulation management algorithm based on FFP and platelet transfusion guided by TEG (57, 76). Our experience shows, that therapy of severe bleeding often requires haemostatic interventions increasing the values of ROTEM parameters (in particular clot firmness) within the upper normal range. For example, while for most patients the primarily targeted FIBTEM A10 value is 9–12 mm, in severe haemorrhage a FIBTEM A10 of ≥15 mm seems to be required (71, 96). However, supernormal levels of FIBTEM A10/MCF are not recommended in order to avoid thromboembolic events (reference range 7–23). Again, the main reason for reduced clot firmness in trauma patients seems to be impaired fibrin polymerisation based on low plasma fibrinogen concentration, disturbed polymerisation due to colloid infusion or factor XIII deficiency, and increased fibrinolysis (88). The required fibrinogen dosage in order to achieve a targeted increase in plasma fibrinogen or FIBTEM A10 (MCF), based on our clinical experience (32, 71), is presented (▶ Tab. 3). Infusion of colloids, especially hydroxylethyl starch,

may result in measuring wrongly elevated plasma fibrinogen levels if plasma fibrinogen concentration is measured by optical methods such as the Clauss' method. Clinical efficacy is crucial, not a change in the results of laboratory testing. The increase in plasma fibrinogen concentration after administration of fibrinogen concentrate has been demonstrated by several authors. In these studies a median fibrinogen increment of 0.2–0.3 g/L was observed per 1 g fibrinogen concentrate administered (in patients with a median body weight of about 80 kg). This increment can be calculated on patients' plasma volume, too. An increment of plasma fibrinogen concentration of 0.25 g/l corresponds to an increase in FIBTEM A10 (MCF) of about 2 mm. Of course, the increment in plasma fibrinogen concentration and FIBTEM A10 (MCF) is dependent on patients' plasma volume, bleeding dynamics, and simultaneous volume therapy with crystalloids and colloids, too (40, 57). Detection of fibrinogen deficiency, decreased to a critical and substitution demanding level (20), is thereby possible within 15 min after patient's arrival in the hospital. Impairment of fibrin polymerisation by colloids, such as hydroxyethyl starch, is also detected by ROTEM analysis, in particular in the FIBTEM assay (27).

6. In acquired deficiency of vitamin K-dependent coagulation factors, the application of PCC may help to restore impaired thrombin generation and to stop coagulopathic bleeding (80, 82) as low prothrombin levels will impair thrombin formation and can be detected by EXTEM's CT (48). In a recently published cohort study including 3865 patients undergoing cardiac surgery, first-line therapy with fibrinogen concentrate and prothrombin complex concentrate guided by POC-testing (ROTEM and Multiplate) was associated with a significant reduction in transfusion requirements, incidence of massive transfusion, re-surgery and thromboembolic events, as well as costs (36). These results could be confirmed recently by a prospective randomised clinical trial in coagulopathic cardiac surgery patients demonstrating a significant reduction in transfusion requirements, transfusion-associate adverse events, and costs, as well as improved outcomes including six-month mortality in the POC compared to the control group (97). In trauma patients this concept was associated with a reduced incidence of multiple organ failure (compared to patients from the German trauma registry) and reduced mortality (observed mortality vs. calculated TRISS and RISC mortality) (69, 82).

7. Following major surgery or trauma, FXIII levels may be low and possibly be responsible for "unexplained" ongoing bleeding (99). This may even happen already intraoperatively (10). Supplementation of FXIII increases clot firmness, accelerates clot formation, and increases clot stability (22, 90).

8. In first-time bleeding, platelet count decreases late due to an increased release of platelets from bone marrow and spleen. However, decline of platelet count is a highly individual phenomenon (59). Of note, with each pooled platelet concentrate the patient will receive 200–350 ml of plasma (10).

9. Detailed analysis of impaired platelets' function is not possible with TEG or ROTEM.

10. If all other therapeutic options fail to stop bleeding in patients with severe haemorrhage treatment with recombinant activated factor VII (rFVIIa) may be considered on a case-by-case decision after correction of concomitant factors. Notably, after the implementation of ROTEM-based POC-algorithms off-label use of rFVIIa could completely be avoided since 2005 at University Hospital Essen. Accordingly, the incidence of off-label use of rFVIIa could be reduced by 92% in the POC group of the prospective randomized clinical trial in complex cardiac surgery performed in Frankfurt (97). This may not only be important with regard to costs-saving but in order to avoid thromboembolic events, too.

Conclusions

Growing consensus points out, that plasma-based coagulation screening tests like aPTT and PT are inappropriate for monitoring coagulopathy or guide transfusion therapy.

While large randomised clinical trials in most clinical settings are still lacking, increasing evidence of more than 5000 surgical / trauma patients – an excellent review can be found in Johansson's article (51) – points towards the beneficial effects of a thrombelastography- or -metry-based approach in diagnosis and goal-directed therapy of perioperative massive haemorrhage.

Further prospective evaluation of ROTEM vs. TEG and an evidence-based determination of the targeted levels are required (85). However, the use of coagulation factor concentrates guided by rapid POC testing using ROTEM or TEG in order to

- correct coagulopathy,
- stop diffuse bleeding timely and
- avoid any unnecessary or inappropriate allogenic blood transfusion at the same time is supposed to be the future of haemorrhage resuscitation (68).

As presented here, results of viscoelastic (and aggregometric) tests should be linked to therapeutic interventions by coagulation management algorithms.

Conflict of interests

HL: travel expenses and lecture fees from CSL Behring GmbH, Mitsubishi Pharma,

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