



Rotational thromboelastometry-guided trauma resuscitation

Damian D. Keene, Giles R. Nordmann, and Tom Woolley

Purpose of review

Haemorrhage from major trauma is a significant cause of death worldwide. The UK Defence Medical Service (UK-DMS) has had significant experience in managing severely injured and shocked trauma casualties over the last decade. This has led to the integration of rotational thromboelastometry (ROTEM) into damage control resuscitation delivered at Camp Bastion Field Hospital in Afghanistan. This review aims to describe the rationale for its use and how its use has evolved by UK-DMS.

Recent findings

Although there is reasonable evidence showing its benefit in cardiac and liver surgery, evidence for its use in trauma is limited. More recent studies and meta-analyses have demonstrated a reduced rate of transfusion and blood loss, but no benefit on mortality. Despite this, there is a growing body of opinion supporting ROTEM use in trauma with European guidelines supporting its use where available. Recent UK-DMS experience has shown that it is a fast, reliable and robust means of identifying transfusion requirements.

Summary

ROTEM provides a means to rapidly assess coagulation in trauma casualties, allowing targeted use of blood products. It provides information on clot initiation strength and breakdown. However, its use in trauma has still to be fully evaluated.

Keywords

coagulopathy, rotational thromboelastometry, trauma

INTRODUCTION

Major trauma is a significant cause of death worldwide leading to 5 million deaths annually [1^{**}]. A large proportion of deaths are due to bleeding, with haemorrhage accounting for 80% of deaths in the operating theatre and 40% of all deaths from trauma within the UK [2,3]. It is generally accepted that a proportion of patients arriving in emergency departments have significant coagulopathy prior to any medical interventions [4,5]. This is independent of fluid administration, acidosis and hypothermia and is termed acute trauma coagulopathy (ATC) [6,7]. The mechanisms for ATC remain unproven, but appear to be linked to tissue shock [8]. ATC is further exacerbated if haemodilution, acidosis and hypothermia are allowed to occur [9]. The global term for these effects is trauma-induced coagulopathy (TIC). ROTEM can potentially be used to target coagulation therapy to individualize treatment of TIC.

WHAT IS ROTATIONAL THROMBOELASTOMETRY?

Rotational thromboelastometry (ROTEM) is a near patient test measuring the viscoelastic properties of whole blood. It is based on the technique of thromboelastography (TEG) developed by Professor H. Hartert in 1946. In ROTEM, a rotating pin is inserted into a cuvette containing 340 μ l of citrated whole blood. As clot begins to form, pin movement is inhibited. The degree of inhibition is displayed in real time on the ROTEM screen, with preset parameters displayed as the test progresses (Fig. 1) [10–12].

Department of Military Anaesthesia and Critical Care, Royal Centre for Defence Medicine, Birmingham, UK

Correspondence to Lt Col Tom Woolley, FRCA, RAMC, Department of Anaesthesia, Plymouth Hospitals NHS Trust, Derriford Road, Crownhill, Plymouth, Devon PL6 8DH, UK. Tel: +44 1752202082; e-mail: tomwoolley@me.com

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KEY POINTS

- The causes of trauma-induced coagulopathy are multifactorial and require concurrent correction of all contributing factors.
- ROTEM provides a rapid, contemporaneous assessment of clotting in acute bleeding that may help target therapy to reduce coagulopathy.
- Using CA10 allows for fast and reliable prediction of EXTEM and FIBTEM maximum clot firmness.
- ROTEM has been shown to be useful in trauma and its use has been recommended by the European Society of Anaesthesiologists.

ROTEM is initiated by the addition of reagents to the cuvette using an automated pipette as indicated by on-screen instructions. Clot formation is initiated by the addition of calcium and either tissue factor, to mimic the extrinsic pathway (EXTEM), or ellagic acid to mimic the intrinsic pathway (INTEM). Further reagents are added to investigate specific aspects of the coagulation process. Cytochalasin D, a platelet inhibitor, can be added making the resultant trace dependent on fibrin formation and polymerization alone (FIBTEM). Addition of aprotonin can assess the extent of fibrinolysis (APTEM), whereas the addition of heparinase can assess any heparin effect (HEPTTEM).

BACKGROUND

It has been well demonstrated that ROTEM values correlate with platelet and fibrinogen levels in

multiple surgical populations [13–15] and that results are available significantly faster than standard laboratory tests [12,16–18].

As results are available more rapidly, this reduces the time between blood samples being taken and any intervention being delivered [14,16]. In the patient with ongoing blood loss, rapid test turn around is vital to avoid results becoming historical.

Studies in cardiac surgery have demonstrated that ROTEM-guided transfusion is cost-effective due to a significant decrease in blood product usage [19–23]. A reduction in postoperative bleeding after cardiac surgery has also been shown, but this is not universally the case [21,23,24]. However, a recent meta-analysis of randomized trials in cardiac and liver surgery showed a decrease in blood loss with ROTEM or TEG use, but no decrease in mortality [25].

A health technology cost analysis of ROTEM use published in 2008 concluded that there is strong evidence for ROTEM use in cardiac and liver surgery. Its use in trauma was recommended, although it was acknowledged no randomized trials of its efficacy exist [26]. More recently, a large observational study demonstrated a significant reduction in transfusion requirements of fresh frozen plasma (FFP), platelets and packed red blood cells (PRBC) on the implementation of ROTEM for goal-directed therapy in all high-risk surgeries as well as a reduced rate of massive transfusion [27].

Studies looking specifically at ROTEM use in trauma are limited to retrospective observational studies. They have demonstrated a significant reduction in the number of units transfused as well as a reduction in blood loss, but no effect on mortality [28,29]. Conducting randomized controlled trials

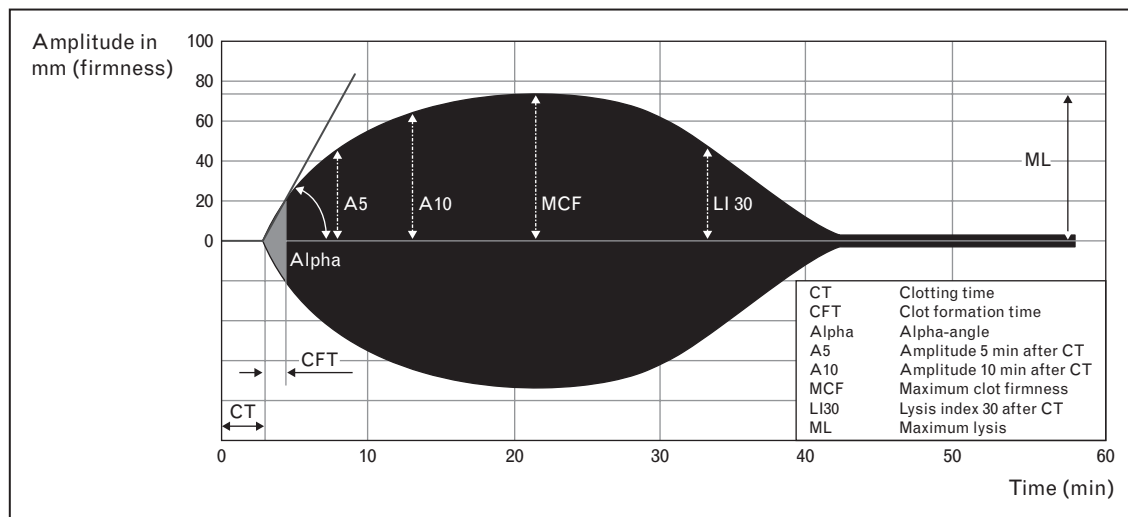


FIGURE 1. Classical rotational thromboelastometry (ROTEM) trace (Tem International GmbH) and parameter definitions [10–12]. Website: www.rottem.de.

(RCTs) looking at interventions in bleeding trauma patients has proven to be difficult due to the heterogeneity of injury and clinical management as well as difficulty in recruitment [30]. Curry *et al.* [30] identified 35 RCTs with only the Crash 2 study that evaluated the use of tranexamic acid in trauma (with >20000 patients) demonstrating a significant survival advantage. Hence, despite the lack of evidence demonstrating improved mortality, recent European reviews on the management of bleeding have recommended ROTEM use in trauma where available [1²,2,31].

UK-DMS opted to use ROTEM rather than TEG (Haemoscope Corp., Braintree, Massachusetts, USA) after initial evaluation at the Defence Science and Technology Laboratory (DSTL), Porton Down. ROTEM was perceived to be more physically robust and to have a more intuitive interface for the infrequent user.

In 2009, ROTEM was deployed to Afghanistan as part of a feasibility study. It was determined to be clinically useful, identifying more coagulopathic patients and providing faster results compared with standard laboratory tests [prothrombin time (PT), activated partial thromboplastin time (aPTT)] [32]. In UK-DMS, damage control resuscitation EXTEM and FIBTEM are performed, ideally with a platelet count and blood gas analysis.

CURRENT UK DEFENCE MEDICAL SERVICE RESUSCITATION PRACTICES

There has been a significant evolution over the last decade in the management of haemorrhage after trauma in both civilian and military institutions [33–35]. Consensus has driven a move towards early haemorrhage control with simultaneous protocol-guided resuscitation using blood products, establishing targeted coagulation therapy as soon as possible [36,37].

UK-DMS goals during resuscitation are two-fold. First is to reverse tissue shock early with volume replacement. This is guided by correction of base excess and lactate as surrogate markers of tissue perfusion rather than restoration of an arbitrary blood pressure. The second goal is to optimize coagulation by correction and maintenance of normal ROTEM parameters coupled with a fibrinogen more than 2 g/dl, platelet count more than 100 g/dl, temperature more than 36°C, ionized calcium more than 1 mmol/l and a K⁺ less than 4.5 mmol/l.

The targets set out above are the minimum levels to be maintained during resuscitation. In the casualty with ongoing bleeding, component therapy should anticipate need, rather than wait

for abnormal laboratory results to prompt therapy. This may necessitate the administration of blood components even when results are normal in order to ensure they do not fall below the specified targets. Thus, once the ROTEM has been normalized, it should not become abnormal again.

During the initial stages of resuscitation, the massive haemorrhage protocol and clinical guidelines for operations are followed using FFP and PRBC at a ratio of 1:1 for blood product resuscitation [34,38]. The initial trauma blood panel includes iSTAT blood gas analysis (Abbot Laboratories, Abbott Park, Illinois, USA), ROTEM (EXTEM and FIBTEM), full blood count and a clotting screen (PT, aPTT). The initial ROTEM provides a starting point, similar to that of the initial base excess and lactate. An unexpectedly abnormal ROTEM, especially in the less severely injured casualty, should alert the clinician to the possibility of significant unrecognized injury.

Once bleeding is controlled, a switch to targeted transfusion is made. Further transfusions of cryoprecipitate and platelets are guided by ROTEM and laboratory platelet and fibrinogen levels.

Interpretation of rotational thromboelastometry

ROTEM should not be interpreted in isolation; the clinical condition of the casualty must always be considered to put results in context.

Pattern recognition plays an important role in basic ROTEM interpretation. Often the shape of the curve will provide more information than measured values (Fig. 2). These patterns shown represent grossly abnormal coagulation and may take 30 min or more to become apparent. In order to detect more subtle abnormalities, a more systematic analysis is required as described below.

EXTEM should be examined first assessing clot initiation (clotting time, CT) followed by clot strength (maximum clot firmness, MCF). This should then be analysed alongside FIBTEM. Finally, an assessment of fibrinolysis should be made.

Clot initiation (EXTEM clotting time)

A prolonged CT represents slow clot initiation. EXTEM CT more than 80 s has been shown to correlate with a fall in clotting factor II, VII and X levels to below 35% of normal [39]. Therefore, FFP should be administered to maintain an EXTEM CT less than 80 s (normal range 42–74 s). In our experience, the requirement for additional FFP is infrequent, possibly due to its ongoing use as volume replacement during resuscitation.

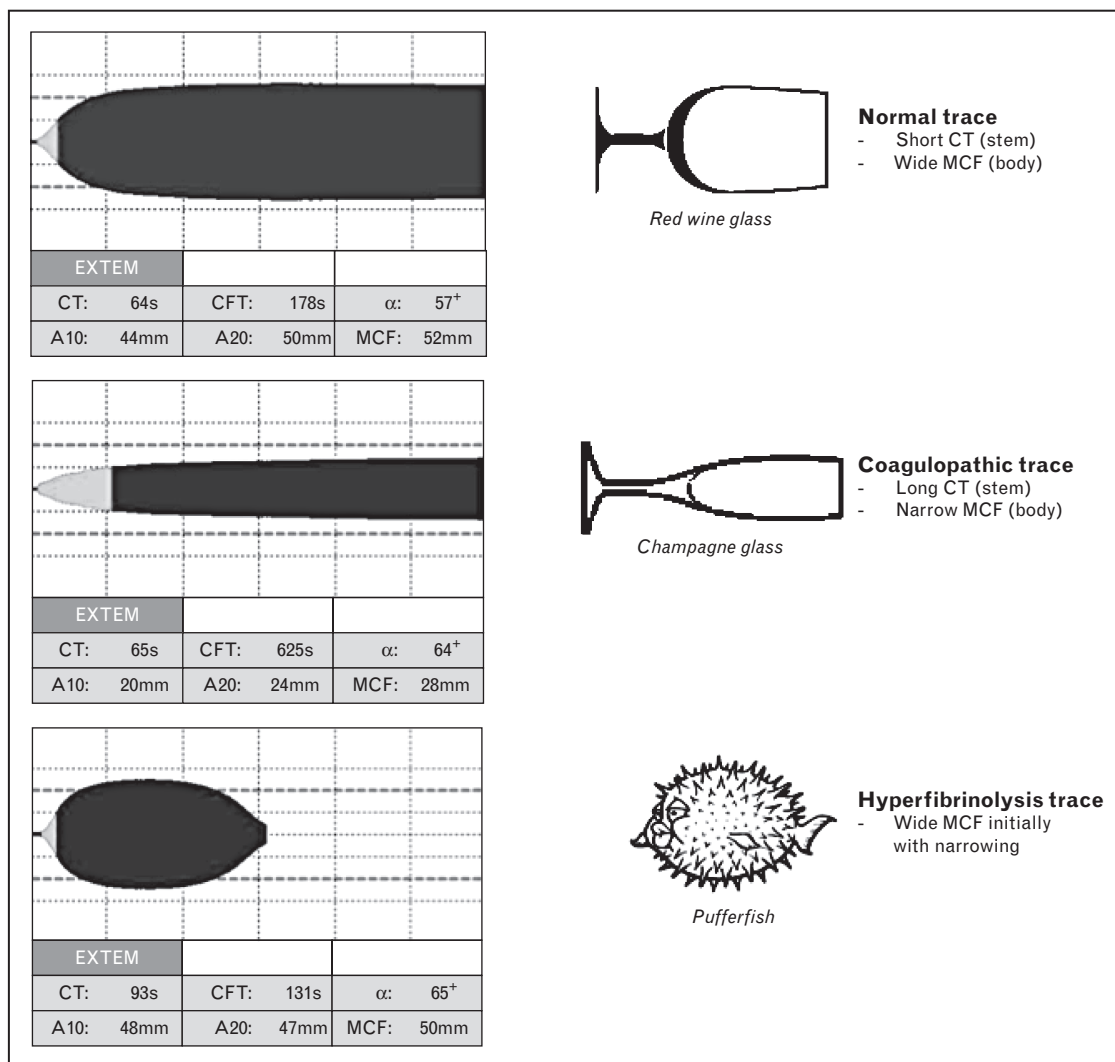


FIGURE 2. Global trace patterns.

Clot strength (EXTEM maximum clot firmness and FIBTEM maximum clot firmness)

EXTEM MCF is a measure of maximal clot strength, which is dependent on platelet number and function as well as fibrinogen levels. FIBTEM MCF, however, is solely a measure of fibrinogen levels. A low EXTEM but normal FIBTEM MCF implies either lack or dysfunction of platelets. This can easily be differentiated by a platelet count, a normal count implying platelet dysfunction. There is increasing speculation that platelet dysfunction has a role in ATC [17,40,41]; however, rates are as yet unclear. Davenport and Brohi [40] showed that in civilian trauma patients, the majority had counts above 100 on admission, but still show signs of platelet dysfunction. There are no data from Afghanistan currently looking at the rate of platelet dysfunction.

A low EXTEM and FIBTEM MCF indicates a lack of both functional platelets and fibrinogen. An estimation of the relative contribution of platelets and fibrinogen should be made in conjunction with a platelet count. There is good evidence to show that increasing fibrinogen levels will increase EXTEM MCF independent of platelet count, thereby reducing the need for platelet transfusion [42] and so it may well be preferential to administer cryoprecipitate rather than platelets.

FIBTEM MCF has been shown to correlate well with laboratory fibrinogen levels [13]. A FIBTEM MCF of 7 mm correlates with a fibrinogen of 1.5 g/l, with MCF levels less than 7 mm associated with profuse bleeding [13,43]. The UK-DMS target for Clauss fibrinogen is more than 2.0 g/l; we, therefore, aimed to maintain a FIBTEM clot amplitude at 10 min (CA10) more than 10 mm by administration of cryoprecipitate. Clauss fibrinogen is used alongside FIBTEM to

allow operational flexibility, as ROTEM may not always be available and to provide a means to audit the accuracy of FIBTEM in this environment.

Early assessment of maximum clot firmness

In a coagulopathic patient, it may take 30 min to reach MCF, significantly lengthening the intervention time [17]. It has been well documented that the clot amplitude at 5 and 10 min (CA5 and CA10) can accurately predict the final MCF of both EXTEM and FIBTEM [17,44]. Therefore, CA5 or CA10 can be used to assess clot strength earlier. Unlike other institutions [45], UK-DMS has not set numerical targets for intervention; however, an EXTEM CA10 of less than 35 mm or a FIBTEM CA10 of more than 10 mm is generally seen as a treatment threshold. UK-DMS has chosen not to have specified values for intervention as our aim is to maintain a normal ROTEM rather than react to the abnormal. This may require transfusion with a normal ROTEM if the trend is towards coagulopathy.

Hyperfibrinolysis

A maximum lysis of 15% is by definition hyperfibrinolysis. Maximum lysis is a measure of the difference between MCF and the clot firmness when the test is stopped. It cannot be compared in tests stopped at different times; even in a normal individual, more lysis will occur with time. It is more robust to use the lysis index at 30 min (LI30) to evaluate the effect of any treatment. This is the amount of clot remaining at 30 min and should be more than 94%. It should be noted that the ROTEM trace shows the net effect of clot formation and clot breakdown. There may well be significant fibrinolysis occurring; however, if there is an increased amount of clot formation, there may well be a normal trace. Recent evidence suggests that ROTEM may be insensitive at detecting hyperfibrinolysis and that higher levels of fibrinolysis are associated with significantly worse transfusion requirements, morbidity and mortality [46,47]. The presence of hyperfibrinolysis on ROTEM definitely requires treatment; however, a normal ROTEM should not necessarily prevent administration of tranexamic acid.

Timings and indications for rotational thromboelastometry analysis

ROTEM analysis should occur on admission as a baseline and should be repeated throughout the resuscitation. UK-DMS guidelines suggest not less than every 30 min while resuscitation is ongoing.

ROTEM should be performed 15–30 min after any intervention to confirm efficacy of treatment.

Limitations

Although the test is performed on a whole blood sample, it is performed *in vitro* without the presence of the vascular endothelium. Activation of the vascular endothelium is implicated in the development of ATC and, therefore, any in-vitro tests must be interpreted with care.

It is important to assess calcium levels and temperature whenever interpreting ROTEM as the analysis is performed at 37 °C with the addition of calcium to the sample. The effect of neither hypocalcaemia nor hypothermia on clotting will be demonstrated by ROTEM, meaning a normal ROTEM would be falsely reassuring in these circumstances.

The effects of antiplatelet medications such as aspirin and clopidogrel are not detected by ROTEM as the thrombin levels generated by test initiation overcome their inhibitory effects [48]. The effects of these agents will only be detected by platelet aggregation [49]. This is not usually a concern in the military population, but must be borne in mind in civilian practice as a reason for ongoing bleeding with apparently normal ROTEM and standard laboratory tests.

Case studies

The following case studies demonstrate how ROTEM has been used to direct haemostatic resuscitation. In the first case in 2009, ROTEM was performed but not used to guide transfusion. The second case demonstrates the part it now plays in UK-DMS resuscitation strategies. A summary of each case's injuries, prehospital treatments and presenting physiological parameters can be seen in Table 1. Both casualties had massive injuries and required immediate surgery to gain rapid haemorrhage control.

Case 1

Surgery was performed as part of the initial resuscitation following damage control principles. Due to the extent of injury, the initial resuscitative surgery took over 2.5 h, during which time the casualty received 24 PRBC, 18 FFP, one pool of platelets and one pool of cryoprecipitate. At this stage, the casualty was clinically profoundly coagulopathic (as can be seen on ROTEM) and was transferred to ICU for 2 h to allow stabilization before completion of surgery (Fig. 3). Surgery was completed after a further 2.5 h in the operating room. On return to

Table 1. Injury, prehospital and physiological parameter: summary of cases

	Case 1	Case 2
Sex	Male	Male
Age	26	25
Mechanism of injury	Improvised explosive device	Improvised explosive device
Major injuries	Right through knee amputation; left above knee amputation	Right below knee amputation; left above knee amputation; amputation right arm
Prehospital time (min)	40	35
Prehospital treatment	Tourniquets	Tourniquets; 1 FFP, 1 PRBC, 1 g TXA
Admission HR (bpm)	110	No pulse
SBP (mmHg)	52	No radial
GCS	15	13
pH	7.32	6.67
Base excess (venous)	-5	<-30
Platelet count	250	185

FFP, fresh frozen plasma; GCS, Glasgow Coma Score; HR, heart rate; PRBC, packed red blood cell; TXA, tranexamic acid.

the ICU, microvascular bleeding continued requiring further resuscitation with blood products as guided by standard laboratory tests. In total, over

a 12-h period, the patient received 31 PRBC, 28 FFP, three pools of platelets and three pools of cryoprecipitate.



FIGURE 3. Sequential rotational thromboelastometry (ROTEM) traces for each case. Tables show relevant blood results taken at the time of starting each trace and the total blood products delivered to that point.

Case 2

Rapid surgical control of bleeding was obtained with a laparotomy and clamping of the left internal iliac artery. Surgery was then paused to allow further resuscitation and warming. Two pools of platelets and two pools of cryoprecipitate were administered in response to a low-amplitude MCF on both the EXTEM and FIBTEM (Fig. 3) with a platelet count of 86 g/dl. Once stabilized, a computed tomography scan was performed followed by a return to surgery 3.5 h after admission. Ongoing surgery required further targeted blood product administration. Despite an EXTEM MCF remaining within the normal range, two pools of platelets were given due to a laboratory platelet count of 32 and anticipated further significant blood loss.

Surgery was completed after a further 4 h. The casualty remained stable with a normal base excess and improving lactate. ROTEM parameters remained stable with a small increase in CT, clot formation time and reduction in MCF noted prior to dressing of wounds (all within normal range). No evidence of ongoing bleeding was noted and no further blood loss anticipated; therefore, no further blood products were given. A lumbar epidural was sited prior to transfer to the ICU, 7 h and 45 min after injury, where the casualty was extubated 2 h later. In total, over 8 h they received 18 PRBC, 17 FFP, four pools of platelets and two pools of cryoprecipitate.

CONCLUSION

Although the mechanisms of TIC are not fully understood, what is clear is that it is multifactorial and constantly evolving during resuscitation. ROTEM provides a means to aid in clinical decision-making in the rapidly changing environment of transfusion-based resuscitation. It provides information not just on clot initiation, but also on clot strength and breakdown. Although definitive evidence that ROTEM-guided resuscitation reduces mortality is still needed, we can be assured it enables a more accurate and rapid appreciation of the needs for clotting factor, fibrinogen and platelet therapy than conventional laboratory-based coagulation monitoring.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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