Thromboelastography

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1 Introduction

Perioperative haemostatic monitoring is important to diagnose potential causes of haemorrhage, to guide rational choices of haemostatic therapies, to estimate the risk of bleeding during surgical procedures. Currently, laboratory-based tests are the mainstay in assessing coagulation status. These include typically, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, international normalised ratio (INR), platelet count.

Problems with routine tests include turnaround time (TAT) but more importantly these are performed on plasma rather than whole blood, yielding no information on platelet function. These tests are performed at standard temperature of 37° rather than patient temperature, which is important under certain circumstances e.g. cardiac surgery.

2 History

Thromboelastography was first described in 1948 by Hartert of Heidelberg during World War II, as a method to assess global haemostatic function from a single blood sample; this was the original Hellige thromboelastography. Calatzis et al, 1996 have further elaborated on the principles using different activators and inhibitors to localise haemostatic disorders within a short space of time.

Rotational thromboelastography (ROTEM) is a refinement of the principle developed in Ludwig-Maximillian University of Munich.

2.1 Terminology

Thromboelastography, TEG are used generically in literature. Thromboelastograph and TEG are registered trademarks of the Haemoscope Corporation (Niles, IL) and are used, since 1996 for assays performed by their instruments.

ROTEM, TEG/ROTEM are trademarks registered to Pentapharm GmbH (Munich, Germany), refer to assays from their own instrumentation viz. rotation thromboelastometry.

3 Point of care monitoring

Point of care (POC) monitoring overcomes several of the limitations. Various devices assessing viscoelastic properties of whole blood are available include thromboelastography (TEG®), rotation thromboelastometry (ROTEM®), Sonoclot® analysis. Benefits of these devices include:

- coagulation status of whole blood is assessed: in vivo coagulation system interactions with platelets and red blood cells (RBC)
- useful information on platelet function
- real-time clot development visually displayed
- analysis at patient temperature

Several important limitations must be considered, however: in vivo and in vitro coagulation have important differences

- static, no flow conditions
- cuvette is unlike an endothelialised blood vessel

4 Devices

4.1 TEG

Assesses viscoelastic properties under low shear conditions. It uses a stationary cylindrical cup that holds the blood sample of 360mL (0.36ml) and oscillates through an angle of 4°45'. Each rotation lasts 10s. A pin is suspended in the blood sample by a torsion wire and is monitored for motion.

The torque of the rotation cu is transmitted to the immersed pin after fibrin-platelet bonding has occurred, linking the cup and pin together. The strength of the fibrin-platelet bonds affects the magnitude of the pin motion. The output is thus directly related to the strength of the formed clot.

With clot retraction and lysis the fibrin-platelet bonds are broken and the transfer of motion diminishes.

The rotation movement of the pin is converted by an electromechanical to an electrical signal which is displayed as a TEG tracing.

4.2 ROTEM

ROTEM uses a modification of the TEG: the signal of the pin is transmitted using an optical detector system and not a torsion wire, the movement originates from the pin itself and not the cup. The ROTEM also has an electronic pipette which improves reproducibility and performance.
A typical device has four independent measuring channels, each providing a thromboelastometry (TEM) trace which can be by a computer.

4.2.1 INTEM
INTEM is a baseline test using ellagic acid contact activator for analyzing general coagulatory status of the patient. Clotting time (CT) and clot formation time (CFT) allow for the analysis of factor deficiencies or detection of the presence of anticoagulants.

One limitation of the standard ROTEM analysis is the inability to measure platelet adhesion defects or aspirin-like defects during primary haemostasis.⁸

4.2.2 HEPTEM
HEPTEM add heparinase to demonstrate heparin or a residual heparin effect if compared to INTEM test, or coagulation be tested in the presence of heparin (if present in the sample).

4.2.3 FIBTEM
FIBTEM test fibrinogen concentration and polymerisation alone, in the absence of platelets. Cytochalasin D is used as a platelet inhibitor. In the example below patient B has a normal FIBTEM trace, in view of the abnormalities in the INTEM (maximum clot firmness, MCF, CT, CFT) platelets were necessary. (In⁹)
4.3 Variations and modification

4.3.1 Heparinase coated cups
Under conditions where heparin is administered systemically e.g. during CPB, vascular surgery, the effect of heparin can be neutralised by using heparinase coated cups. This will also neutralise heparin like substances. [2]

4.3.2 Celite activation
Celite accelerates the activation process, allowing a meaningful result to be obtained quickly. This analysis has supplanted native blood in many situations and has been widely validated.

4.3.3 Activator F, ADP, arachidonic acid
Activator F is a proprietary reagent consisting of Reptilase and FXIIIa. If Act F is added to a sample taken in heparinised tube (thrombin inhibited) a fibrin network is generated independent of thrombin. In the absence of platelet activation there is a minimal response on TEG curve (low MA). Platelet activators ADP and arachidonic acid (AA) can be added to provide alternate mechanisms of platelet activation, and thus increase MA on the trace. The effect of antiplatelet drugs can therefore be assessed and quantified by comparing an unmodified trace and one where platelet activators (ADP, AA) have been added as in Swallow et al.[11, 30]

4.3.4 Platelet-mapping kit
System marketed by Haemoscope as Platelet-Mapping Kit which uses the modified TEG tests in Table 1 to assess platelet function in the presence of inhibitors like aspirin and clopidogrel. It has been used to map time dependant effect of these agents on platelet function by Swallow et al.[30]
The results compare favourably to other platelet function tests like PFA-100 and optical agggregometry – which is considered the gold standard. The benefit of this kit is that it is a bed-side test with result available in 20-30min.

5 Activation
Various test, with different activators and reagents are available. Different tests interrogate different aspects of coagulation under varying conditions:

- Extrinsic : tissue factor ex-TEM
- Intrinsic : contact activator in in-TEM
- Fibrinogen levels in the presence of platelet inhibitor : cytochalasin D in fib-TEM

5.1 Measurements
They measure and display viscoelastic changes at all stages of the evolving and dissolving clot. On a time scale they display :

- time to initial fibrin formation (TEG reaction time, r ; ROTEM clotting time, CT)
- kinetics of fibrin formation and clot development
- strength and stability of fibrin clot
- clot lysis (fibrinolysis)

Table 1 from [11]

<table>
<thead>
<tr>
<th>Table 1</th>
<th>retrievable changes to standard TEG®.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagent used</td>
<td>Rationale for use</td>
</tr>
<tr>
<td>Citrate</td>
<td>Enables prolonged storage of samples before analysis.</td>
</tr>
<tr>
<td>Heparin</td>
<td>Inhibits thrombin allowing the contribution of fibrin and platelets to be assessed.</td>
</tr>
<tr>
<td>Heparinase</td>
<td>Reverses the effect of heparin, e.g. in patients on cardiopulmonary bypass.</td>
</tr>
<tr>
<td>Activators (e.g. Celite, Kabi, Tissue Factor)</td>
<td>Speed up result acquisition.</td>
</tr>
<tr>
<td>Glycoprotein</td>
<td>Inhibit platelet function allowing the contribution of fibrinogen to be assessed.</td>
</tr>
<tr>
<td>Hb/IIa inhibitors</td>
<td>Reverse fibrinolysis.</td>
</tr>
<tr>
<td>Antifibrinolytic drugs (e.g. Tranexamic acid, Activator F [Reptilase] and Factor XIIa)</td>
<td>Activates fibrin formation without affecting platelets.</td>
</tr>
<tr>
<td>Arachidonic Acid</td>
<td>Activates platelets via the production of thromboxane A2. This pathway is affected by aspirin.</td>
</tr>
<tr>
<td>ADP</td>
<td>Activates platelets via P2Y1 and P2Y12 receptors. Clopidogrel and other thienopyridines inhibit the P2Y12 ADP receptor.</td>
</tr>
</tbody>
</table>

Figure 5 from[9]
Table 2 below lists important values and reference ranges for both instruments.

Table 2. Nomenclature and Reference Values for Thrombelastography (TEG®) and Thrombelastometry (ROTEM®)

<table>
<thead>
<tr>
<th>Clotting time (period to 2 mm amplitude)</th>
<th>TEG®</th>
<th>ROTEM®</th>
</tr>
</thead>
<tbody>
<tr>
<td>R (reaction time)</td>
<td>CT (clotting time)</td>
<td></td>
</tr>
<tr>
<td>N (WB) 4–8 min</td>
<td>N (CT, in-TEM) 135–216 s</td>
<td></td>
</tr>
<tr>
<td>N (Cit, kaolin) 348 min</td>
<td>N (Cit, ex-TEM) 43–74 s</td>
<td></td>
</tr>
<tr>
<td>K (kinetics)</td>
<td>CFT (clot formation time)</td>
<td></td>
</tr>
<tr>
<td>N (WB) 1–4 min</td>
<td>N (CT, in-TEM) 45–100 s</td>
<td></td>
</tr>
<tr>
<td>N (Cit, kaolin) 5.1–7.3 min</td>
<td>N (Cit, ex-TEM) 44–148 s</td>
<td></td>
</tr>
<tr>
<td>Clot-stiffening (alpha angle)</td>
<td>α (slope between r and k)</td>
<td></td>
</tr>
<tr>
<td>N (WB) 47–74°</td>
<td>N (Cit, in-TEM) 71–82°</td>
<td></td>
</tr>
<tr>
<td>N (Cit, kaolin) 52–78°</td>
<td>N (Cit, ex-TEM) 69–91°</td>
<td></td>
</tr>
<tr>
<td>Amplitude (at set time)</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Maximum strength</td>
<td>MA maximum amplitude</td>
<td>MCF maximum clot formation</td>
</tr>
<tr>
<td>Lysis (at fixed time)</td>
<td>CL30, CL60</td>
<td>LYT30, LYT60</td>
</tr>
</tbody>
</table>

5.1.1 fib-TEM
This assay gives a modified MA/MCF, which represents the extent of a fibrin clot in the absence of platelets, i.e. functional fibrinogen. There is good correlation between this assay and laboratory assays of fibrinogen. Furthermore laboratory assays have been shown to report falsely high fibrinogen estimates in the presence of haemodilution with colloids.

5.1.2 Comparisons: TEG and ROTEM
Although the TEG and ROTEM tracings look similar there are important differences in the nomenclature and reference ranges. These differences arise because:
- different cups and pins: ROTEM has plastic components resulting in greater surface charge and more contact activation
- proprietary formulas: coagulation activators are of different composition and concentration

Various discrepancies between the assays have been reviewed by Nielsen. [20] are summarised in the table 3. It is vital that these assays are interpreted based on the specific system that was used, especially in the context of patient management algorithms.

5.1.3 Comparison ROTEM/TEG and Sonoclot
The output of sonoclot oscillating probe is sensitive to viscosity changes, therefore monitors viscosity changes during the initiation of coagulation and clot development, while the TEG/ROTEM systems reflect changes once fibrin-platelet bonding has linked up and pin together.

ACT in sonoclot signature reflect initial fibrin formation, whereas R/CT reflect a more developed later stage of initial clot formation. The ACT values have compared favourably to other ACT analyses (8-9%). The Sonoclot assay however is very sensitive to age, sex, platelet count.

6 Clinical uses
These devices have been used in various clinical contexts from laboratories initially as a research tool to perioperative coagulation management. The resurgence in popularity began with their application in liver transplantation and cardiac surgery. They have since found emerging role in trauma, obstetric, cardiology and many other fields of medicine.

6.1 Cardiac surgery
Complexities of coagulation management in patients undergoing cardiac surgery are well documented. A balance need to be found between anticoagulation for CPB and haemostasis after CPB. Further complexity is added by the aggressive use of anti-platelet therapies; CPB initiates complex inflammatory reactions that result in coagulation abnormalities, platelet dysfunction and fibrinolysis. Known contributors include:
• hypothermia
• actions of heparin
• excessive or inadequate protamine administration
• haemodilution: CPB priming
• excessive fibrinolysis
• depletion of coagulation factors
• reduction in platelet numbers and function: contact activation, damage (pumps, oxygenators)
• pre-operative anti-platelet medication

The complex process of anticoagulation with heparin and heparin antagonism with protamine and management of post-operative haemostasis can be guided by these POC tests. Evidence of significant cost benefit, fewer re-explorations, less exposure to blood products is emerging. Avidan et al. in their study note wide discrepancy in transfusion practices, mostly based on local beliefs than evidence, some practices being harmful.[2]
6.1.1 Predictive value
As a predictor of excessive bleeding post-CPB these POC devices have been found to be poor. However they have a high negative predictive value i.e. where viscoelastic tests are normal bleeding is unlikely to be due to a significant coagulopathy. Their place seems therefore to be early identification and targeted treatment of surgical bleeding.

Avidon et al [2] in their study comparing laboratory based algorithm, POC device based algorithm and physician discretion arrived at the following conclusions:
- POC algorithms were not superior to laboratory based algorithms
- POC tests do not predict bleeding
- POC and laboratory algorithms significantly reduced usage of blood products compared to physician discretion
- POC algorithms may be beneficial in rapid weaning, extubation, and discharge where laboratory turn around times are high
- algorithms and guidelines, strictly adhered to avoid unnecessary transfusions

There were important limitations to the study: single center, historical controls were used, POC algorithm may have been inadequate. The study did however support use of POC devices in reducing transfusion, which has been found by other investigators. [25,27]

Anderson et al instituted a similar protocol (see appendix) in the post-op period and were able to demonstrate significant results summarised in table 5, which they subsequently were able to sustain after the study period. Their ICU discharge data was unchanged in both study periods. They suggested that it was the more targeted, earlier and appropriate interventions guided by ROTEM introduction that mostly accounted for their results, as opposed to the speculative use of blood products which had been prevalent.

<table>
<thead>
<tr>
<th>Transfusion requirements before and after the introduction of ROTEM®</th>
<th>Before introduction of ROTEM®</th>
<th>After introduction of ROTEM®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients transfused with CRCs (a)</td>
<td>294/488 (60%)</td>
<td>270/502 (53%)</td>
<td>0.040</td>
</tr>
<tr>
<td>CRCs transfused (units)</td>
<td>1094, 2 (3)</td>
<td>991, 1 (2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Patients transfused with FFP (a)</td>
<td>81/488 (17%)</td>
<td>60/502 (12%)</td>
<td>0.037</td>
</tr>
<tr>
<td>FFP transfused (units)</td>
<td>343, 0 (0)</td>
<td>271, 0 (0)</td>
<td>0.036</td>
</tr>
<tr>
<td>Patients transfused with platelets (a)</td>
<td>77/488 (16%)</td>
<td>56/502 (11%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Platelets transfused (units)</td>
<td>96, 9 (0)</td>
<td>75, 0 (0)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

CRC, concentrated red cells; FFP, fresh frozen plasma.

Frequency data (patients transfused with CRCs, FFP, and platelets) are presented as n (%), data which are continuous but not normally distributed (units of CRCs, FFP and platelets transfused) are presented as absolute number, median (interquartile range).

Table 5 from [3]

6.1.2 Surgical bleeding
Multifactorial and often difficult to identify. Standard laboratory based assays may not identify important causes such as fibrinolysis and platelet dysfunction. Treatment in the post CPB scenario may largely be empirical, with further protamine and blood product (fresh frozen plasma FFP, platelets, cryoprecipitate) being common.

6.1.3 Drug monitoring
TEG has been used successfully to monitor clotting during CPB where direct thrombin inhibitors have been used: Pivalizza, 2002 describes a case of a patient with heparin induced thrombocytopenia (HIT) who needed urgent revascularisation, in the absence of any reliable test for hirudin effect, they were able to use TEG monitoring throughout CPB process. [38]

6.2 Cardiology

6.2.1 Aspirin effect
The percentage inhibition due to aspirin can be quantified by comparing the unmodified curve in the presence of thrombin, i.e. maximal platelet activation, the heparinised sample with Activator F (Reptilase and Factor XIIIa) alone (no platelet activation) and a modified trace with arachidonic acid (AA) stimulation i.e. residual platelet activation with AA in the presence of aspirin. [11]

6.2.2 Clopidogrel and GPIIb/IIIa antagonist
In a similar fashion to aspirin clopidogrel and abciximab effect on platelets can be assessed using ADP-induced platelet aggregation. The Platelet Mapping Kit has been used for this. It has found application in the context of stenting and assessment of stent thrombosis. [11]

Applications for this test kit include:
- diagnosis & management of clopidogrel and aspirin resistance
- tailoring and individualising anti-platelets therapy
- optimising withdrawal of anti-platelet therapy in the peri-op period

6.2.3 Thrombotic events
McCrath et al [37], 2005 investigated the risk of thrombotic events in 240 non-cardiac post-operative patients using TEG. They found an increased risk in those with MA>68mm.

Gurbel et al, 2005 [36] also showed an increased thrombotic risk in patients with increased MA on TEG both pre- and post-loading with clopidogrel at the time of PCI. They developed a predictive tool using TEG parameters of
shortened R time and increased MA correlating to an increased odds ratio for ischaemic events within 6 month of PCI.

6.3 Hepatic surgery
Patients undergoing hepatic surgery, particularly orthotopic liver transplant (OLT) may have significant derangements in their coagulation making POC coagulation monitoring ideal. Major contributors to coagulopathy include:

- defective organ: decreased synthesis and clearance clotting factors
- platelet defects
- systemic complications: sepsis, DIC
- anhepatic phase: hyperfibrinolysis
- immediately after organ reperfusion: explosive hyperfibrinolysis due to accumulation of tissue plasminogen activator, release exogenous heparin, release heparin-like substances
- dilutional: massive blood loss, massive transfusion
- dynamic blood volume changes

Kang et al, 1985 gave the first account of intraoperative haemostatic management using TEG[16]. They compared two groups of transplant patients: TEG guided transfusion, non-monitored/physician discretion. Results and interventions of a patient from the TEG are shown in figure 7 illustrates the effectiveness of TEG guided monitoring.

Notwithstanding improved surgical techniques, Kang et al concluded that TEG monitored patients had required significantly less transfusion (33%), and most of had normalised TEG traces by the end of the procedure.

<table>
<thead>
<tr>
<th>Blood products</th>
<th>TEG-monitored patients</th>
<th>Nonmonitored patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells (unit)</td>
<td>17.0 ± 12.9</td>
<td>26.7 ± 23.8</td>
</tr>
<tr>
<td>Fresh frozen plasma (unit)</td>
<td>18.3 ± 12.5</td>
<td>26.7 ± 24.1</td>
</tr>
<tr>
<td>Platelets (unit)</td>
<td>20.8 ± 12.8</td>
<td>14.1 ± 13.7</td>
</tr>
<tr>
<td>Cryoprecipitate (unit)</td>
<td>12.2 ± 14.2</td>
<td>3.9 ± 12.9</td>
</tr>
<tr>
<td>Total blood products (unit)</td>
<td>67.9 ± 43.9</td>
<td>71.4 ± 63.4</td>
</tr>
<tr>
<td>Crystallloid (litre)</td>
<td>10.2 ± 4.5</td>
<td>17.2 ± 8.5</td>
</tr>
<tr>
<td>Total volume infused (litre)</td>
<td>20.2 ± 11.2</td>
<td>31.4 ± 19.2</td>
</tr>
</tbody>
</table>

Values are mean ± s.d. Significantly different from the corresponding values of the nonmonitored patients (P < 0.05).

Table 6 from [16]

6.4 Obstetric care

6.4.1 Post-partum haemorrhage
Post-partum haemorrhage (PPH) is a leading cause of morbidity and mortality in both the developed and developing world, responsible for up to 25% of all maternal deaths, more than 50% of which could be preventable. Rapid diagnosis and early management is imperative to improve prognosis. Uterine atonia usually precedes the development of coagulation disorders, however in some cases e.g. abruptio placentae coagulopathy precede delivery, and is direct cause of PPH. Decrease in fibrinogen level is the most rapid change observed among the markers of coagulation, fibrinogen concentration has been found to correlate well with severity of haemorrhage.

Huissoud et al studied the use of ROTEM device in PPH in a cohort of 91 women, 54 of which had PPH[13]. Using the FIBTEM test they found significant correlations:

![Figure 7 from [16]](image1)

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• median CT was higher in the PPH group
• CA5 and CA15 (clot amplitude 5, 15 min) and MCF were lower in PPH group
• strong correlation of FIBTEM and fibrinogen levels in both groups
• Hb levels did not seem to affect results as previously reported in literature

CA5 was found to correlate well with fibrinogen levels <1g/l (100% sensitivity, 88% specificity), a finding also in trauma patients (91% sensitivity, 85% specificity).^{[26]}

A fibrinogen value of <2g/l has a predictive value for serious PPH of 100%. In this series fibrinogen <2g/l corresponded to CA5-FIBTEM of 6mm (100% sensitivity, 87% specificity).

<table>
<thead>
<tr>
<th>Fibrinogen levels (g/l)</th>
<th>FIBTEM cut-off values (mm)</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fib &lt; 2</td>
<td>CA5 = 6</td>
<td>100 (100-100)</td>
<td>87 (71-96)</td>
<td>50 (36-64)</td>
<td>100 (100-100)</td>
<td>0.97</td>
</tr>
<tr>
<td>Fib &lt; 1.5</td>
<td>CA5 = 5</td>
<td>100 (100-100)</td>
<td>85 (70-95)</td>
<td>30 (17-43)</td>
<td>100 (100-100)</td>
<td>0.95</td>
</tr>
<tr>
<td>Fib &lt; 1</td>
<td>CA5 = 4</td>
<td>100 (100-100)</td>
<td>86 (71-96)</td>
<td>13 (3-22)</td>
<td>100 (100-100)</td>
<td>0.96</td>
</tr>
<tr>
<td>Fib &lt; 2</td>
<td>CA5 = 6</td>
<td>100 (100-100)</td>
<td>84 (75-94)</td>
<td>40 (32-50)</td>
<td>100 (100-100)</td>
<td>0.96</td>
</tr>
<tr>
<td>Fib &lt; 1.5</td>
<td>CA5 = 5</td>
<td>100 (100-100)</td>
<td>88 (78-97)</td>
<td>33 (22-46)</td>
<td>100 (100-100)</td>
<td>0.97</td>
</tr>
<tr>
<td>Fib &lt; 1</td>
<td>CA5 = 5</td>
<td>100 (100-100)</td>
<td>88 (79-97)</td>
<td>14 (5-24)</td>
<td>100 (100-100)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

AUC: area under curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value

Table 7 from^{[13]}

6.4.2 Pre-eclampsia
Orlikowski et al^{[22,23]} measured platelet counts, TEG parameters and bleeding time in a cohort of healthy pregnant and pre-eclamptic patients. They found MA remained normal (53mm) until the platelet count decreased to less than 54000mm-3 (95% CI, 40-75000mm-3). On this basis they suggested a platelet count 75000mm-3 should be adequate for haemostasis.

6.4.3 Abruption placenta
In a small study by Moopanar et al^{[19]} TEG was found to be insensitive to small changes in coagulation, but sensitivity for major clinically relevant changes was much better. Furthermore hypercoagulability, an early phase of DIC was established by TEG. These investigators highlighted the usefulness for monitoring and treating on-going coagulation defects where laboratory tests are not immediately available.

6.5 Trauma
Coagulopathy is encountered in 25-30% of trauma patients and is associated with worse outcome. It constitutes one of the components of the classic lethal triad of coagulopathy, metabolic acidosis, hypothermia.^{[26]}

6.5.1 Pathophysiology of coagulopathy
Hypothermia act primarily on platelet activation and adhesion by inhibiting the interaction between von Willebrand factor with platelet glycoprotein ib-IX-V complex. It also slows down metabolic rate of coagulation factor enzymes. Clinically significant bleeding occurs in hypothermic and acidic patients in spite of adequate blood, platelet and plasma replacement.^{[31]}

Acidosis has significant effect by inhibiting the action of enzyme complexes on lipid surfaces. At pH 7.0 FVIIa activity is reduced by 90%; FVIIa/TF complex by 55%; the rate of FII (prothrombin) conversion by FXa/FVa conversion is reduced by 70%. The rate kinetics depend on negative charges on exposed phospholipid surface on activated platelets, which are affected by hydrogen ions. The combined effect of acidosis and hypothermia on thrombin generation is profound.

Haemodilution from direct losses (haemorrhage), resuscitation fluid. The situation is aggravated by delays in diagnosing coagulopathy and reconstitution of products.

Hallmarks of established coagulopathy include generalised non-surgical bleeding from wounds, serosal surfaces, skin edges, vascular access sites.
Laboratory tests are often delayed and have inherent limitations: performed on platelet poor plasma, rewarmed to normothermia.\[^{31}\]

### 6.5.2 Usefulness of TEG in trauma

TEG has a place in trauma providing a bedside, point of care test in a dynamic rapidly evolving situation. It provides functional evaluation of overall coagulation on whole blood. Kaufmann et al.\[^{17}\] in a series of 69 blunt trauma patients found 45 (65%) to be hypercoagulable and 7 (10%) to be hypocoagulable, yet in all patients but one the PTT, PT and platelet count were normal. They found a combination of TEG and ISS to be predictive of transfusion in their cohort. Furthermore in the hypocoagulable group was found to have the highest ISS and the most advanced disease necessitating the most urgent aggressive care. The authors noted the simplicity, immediate availability and ability to repeat test in the emergency suite to be particularly appealing.

Rugeri et al. found significant alterations in almost all ROTEM tests in a trauma cohort of 88 patients.\[^{26}\] They were able to determine correlation between standard coagulation tests and ROTEM parameters, and derived transfusion trigger points based on ROTEM parameters alone.

Cutoff values for ROTEM\[^{5}\] parameters

<table>
<thead>
<tr>
<th>Transfusion values</th>
<th>ROTEM[^{5}] Cutoff values</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time &gt; 1.5 of control value</td>
<td>CA[^{5}] _EXTREM = 32 mm</td>
<td>87 (72-87)</td>
<td>100 (99-100)</td>
<td>100 (83-100)</td>
<td>99 (98-99)</td>
<td>0.98</td>
</tr>
<tr>
<td>APPT &gt; 1.5 of control value</td>
<td>CFT-IntlE = 112 s</td>
<td>100 (84-100)</td>
<td>74 (73-74)</td>
<td>23 (19-23)</td>
<td>100 (96-100)</td>
<td>0.94</td>
</tr>
<tr>
<td>Platelets &gt; 50 x 10[^{9}] L[^{-1}]</td>
<td>CA[^{5}] _ FIBTEM = 5 mm</td>
<td>91 (72-93)</td>
<td>85 (84-86)</td>
<td>55 (45-60)</td>
<td>99 (97-100)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Cutoff values were determined according to transfusion threshold values based on standard coagulation parameters. APPT, activated partial thromboplastin time; AUC, area under the curve; CA, amplitude of clot firmness; CFT, clot formation time; NPV, negative predictive value; PPV, positive predictive value.

Table 8 from \[^{26}\]

They also confirmed previous findings of early coagulopathy in up 30% of admission, underlining the relationship between severity of trauma and coagulopathy.

### 7 Problems and limitations of TEG

#### 7.1 Technical

**Sampling**: the sample needs to be processed within 3-4 min of collection, which may necessitate multiple machines in strategic areas of the Hospital rather than a centralised laboratory.\[^{31}\]

**Sampling site** is important: differences between arterial and venous sample have been reported. The sampling need to be consistent.

**Transport of sample** to a central area necessitates using citrated blood to prevent clotting, this has been documented to affect the results.\[^{31,4}\]

**Quality control** outside the laboratory may not be adequate unless specifically trained personnel undertake regular calibration and maintenance.

**Equipment activators** and other modifications are often manufacturer specific making standardisation very difficult.\[^{9}\]

### 7.2 Patient factors

**Gender and age** have been reported have significant differences in the results, although clinical importance of this remains unclear.\[^{10}\] Children were found to have different values compared to adults despite otherwise normal coagulation testing.\[^{24}\] This statistical significance may not necessarily imply clinical significance. Lang et al. reported *female patients* to have faster coagulation activation (shorter CFT and CT), greater clot firmness (higher MCF) and amplitude (CA10 and CA15) compared to males in INTTEM, EXTTEM and FIBTEM tests.

| Cellulocentric Thromboelastography (TEG) values (means ± SD) |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | I. ≤11 months   | II. 12-14 months| III. 15-48 months| IV. 49 months-9 years | V. Adult |
| R (mm)            | 40.1 ± 3.1      | 98 ± 3.3       | 105.5 ± 3.0     | 96 ± 2.5        | 11.1 ± 3.0     |
| K (mm)            | 24.4 ± 3.8      | 25.6 ± 0.6     | 27.2 ± 0.6      | 29.8 ± 0.6      | 27.2 ± 0.6     |
| Angle (degrees)   | 73.2 ± 3.8      | 73.2 ± 3.8     | 71.2 ± 4.2      | 72.9 ± 4.2      | 70.7 ± 3.9     |
| M A (mm)          | 70.2 ± 6.1      | 70.2 ± 6.1     | 68.4 ± 9.2      | 70.8 ± 3.1      | 70.2 ± 1.7     |
| Index             | 2.7 ± 1.6\[^{4}\] | 2.6 ± 1.5\[^{1}\] | 1.9 ± 1.5       | 1.7 ± 1.5       | 1.8 ± 1.4      |
| Fibronectin (%)   | 2.4 ± 3.0\[^{5}\] | 2.4 ± 1.3      | 2.1 ± 1.3       | 2.1 ± 1.4       | 2.0 ± 1.1      |

Table 9

### 8 Conclusion

Viscoelastic POC coagulation analysers are being used in certain clinical situations known for their inherent risk of coagulopathy, especially in cardiac and hepatic surgery. They are finding increasing use in other clinical scenarios like trauma, cardiology in monitoring anticoagulant drugs as well as research.

The next phase of development must include easier handling of blood sample, full automation, simultaneous testing with multiple activators, integrated software analysis and more robust devices.\[^{9}\]
9 Tests for various POC devices

Table 10

10.1 Sonoclot

Sonoclot measures viscoelastic changes in whole blood or plasma samples. A disposable plastic probe(3) is mounted on transducer head(4); the test sample(1) is added to a cuvette(2) which may contain various reagents (activators, inhibitors). The sample is mixed and the probe lowered into the sample, and oscillates vertically. The device measures changes in impedance due to clot formation as a trace, called the sonoclot signature.

10.2 PFA-100

PFA-100 is a whole blood assay that measures the occlusion time of an aperture in a membrane under high-stress and shear condition. A cartridge containing a membrane coated with collagen and ADP or epinephrine is used. The result is reported as closure time.
11 Diagnostic flow chart examples

![Flow chart A](image)

1. CT normal
   - ERD
   - HEPTEM
     - Heparin/LNH
       - Option: Protamine
     - Factor deficiency?
       - Option: FFP
   - CT prolonged

2. CT and MCF
   - Normal
     - ERD
   - Abnormal
     - MCF > 6 mm
       - Intact fibrin network
         - Option: Platelets
     - MCF < 6 mm
       - No intact fibrin network
         - Option: FFP/Cryoprecipitate

Fig. 3. ROTEM® diagnosis flow chart. A. CLOTTING TIME PARAMETERS. The first-line test is an INTEM; if this is normal, no further tests are performed, and excess bleeding is deemed surgical in origin. If clotting time (CT) alone is prolonged, a HEPTEM (addition of heparinase) is performed. If this normalizes the test result, a diagnosis of excess heparin is made, and protamine is administered. Where CT of HEPTEM is also prolonged, a diagnosis of factor deficiency is made – if significant bleeding exists, FFP is ordered. Where INTEM clot formation time (CFT) is prolonged and maximum clot firmness (MCF) reduced, a FIBTEM test is run. If FIBTEM MCF is low, a fibrinogen deficiency is diagnosed and FFP or cryoprecipitate is administered. If the FIBTEM MCF is within the normal range, platelet function abnormality is diagnosed, and platelets are administered if there is significant bleeding. B. CLOTTING TIME/MAXIMUM CLOT FIRMNESS PARAMETERS.

From [1]

12 TEG Patterns

![TEG Patterns](image)

- **Normal**
  - INTEM/INTEM: Normal
  - FIBTEM: Normal

- **Thrombocytopenia or Plasma**
  - INTEM/INTEM: Decreased
  - FIBTEM: Normal

- **Heparin/Coronary**
  - INTEM/INTEM: Decreased
  - FIBTEM: Decreased

- **Hypercoagulation**
  - INTEM/INTEM: Increased
  - FIBTEM: Increased

- **Fibrinolysis**
  - INTEM/INTEM: Normal
  - FIBTEM: Normal

- **DIC**
  - INTEM/INTEM: Normal
  - FIBTEM: Increased

Figure 3a. Perioperative TEG analysis documenting normal preoperative coagulation function. After CPR and permissive hypothermia, decreased MA and α values (demonstrating platelet dysfunction) were accompanied by overmature functional bleeding. Treatment with hirudin and platelet transfusions was required and a value still minimal of bleeding. RCT were all within normal laboratory values in this patient.

From [32]
13 References


