

## ***Perioperative Haemostatic Monitoring: older vs. newer concepts and techniques***

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### **ABSTRACT**

#### **Perioperative Haemostatic monitoring: older vs. newer concepts and techniques**

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Clinical management of acute severe bleeding in the perioperative setting is one of the major challenges for an anesthetic team. The dynamic nature of bleeding calls for rapid diagnosis and immediate interventions. Trauma induced coagulopathy and/or perioperative coagulopathy management is crucial for successful and life saving interventions, involving blood and blood product transfusions in an individualized and rationalized manner. Traditional coagulopathy monitoring using bleeding times offers very little in prediction and guidance during severe bleeding. They are mostly designed for stable patients under anticoagulant treatments and their very long turnaround time renders them impractical for clinical use in this setting. In contrast, viscoelastic devices are designed to assess whole-blood clotting kinetics and whole-blood clot strength and better reflect the interaction between pro- and anti-coagulants, pro- and anti-fibrinolytic factors, and platelets. The most notable advance in haemostatic management using viscoelastic testing is a fibrin-specific clot assessment. The system uses a combination of assays to characterize the coagulation profile for obtaining more detailed information about haemostasis and suggests the cause of the observed coagulopathy. The article offers a thorough and concise presentation of both traditional and viscoelastic methods and techniques in use during severe haemorrhage, followed by a literature review on the use of viscoelastic haemostatic monitoring in different clinical settings.

### **INTRODUCTION**

Clinical management of acute moderate to severe bleeding is one of the major challenges for

an anesthetic team. Though substitution of erythrocytes by transfusion of red blood cells (RBC) is a routine task, adequate maintenance of haemostasis may be considerably more demanding. In fact, the underlying cause of bleed-

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ing and subsequent treatment may be completely different depending on the clinical scenario<sup>1</sup>. The cause of perioperative bleeding is often multifactorial, and its dynamic nature (i.e., major deterioration in a matter of minutes) calls for rapid diagnosis and immediate interventions. Perioperative coagulopathy involves both pro-coagulant and anticoagulant proteins as well as cellular components (i.e. platelets and endothelium). Relatively long turnaround time for conventional hematological testing (>30–60 min) is adequate for managing chronic disorders, but it is crucial to have a faster time (<15–20 min) in perioperative, critically ill patients<sup>2</sup>.

The evaluation of coagulopathy is conventionally performed using prothrombin time [(PT) or international normalized ratio; (INR)], activated partial thromboplastin time (aPTT), fibrinogen level (Clauss method), and Platelet count. These represent the so-called “**Standard Laboratory Tests (SLTs)**”. Some of the limitations of traditional laboratory testing can be overcome by the use of **viscoelastic coagulation testing (VE)**, or **viscoelastic haemostatic assays (VHA)** in whole blood. **Thromboelastometry®** (ROTEM, TEM Innovations, Munich, Germany) and **Thrombelastography®** (TEG; Haemone-tics, Niles, Illinois, USA) are the currently available viscoelastic test devices. SLTs reflect neither the cellular component of haemostasis nor evaluate plasma anticoagulants. SLTs’ relevance is confined to the initiation phase of co-

agulation and measures only the time until generation of the first 2-5% of thrombin. In contrast, VE devices are designed to assess whole-blood clotting kinetics and whole-blood clot strength and better reflect the interaction between pro- and anti-coagulants, pro- and anti-fibrinolytic factors, and platelets.

VE monitoring devices can guide clinicians in more specific haemostatic therapies and fulfill the requirements for a so-called “**Point-of-Care**” (POC) test. POC testing suggests the capability to perform a fast response test at the bedside, easily interpretable and capable to assist decision making for timely interventions. As a consequence, VE monitor-guided haemostatic management may be effective in reducing the number of patients receiving blood products and follow a step by step approach which may lead to a more cost saving management when compared to SLT-based strategies and have a better outcome in terms of unnecessary transfusions avoidance.

## A PIECE OF HISTORY

Despite what one might expect viscoelastic approach to haemostasis is a relatively old issue. After Prothrombin Time (PT) initiation by Armand Quick in 1935, it was Hellmut Hartert in Heidelberg, Germany, in 1948, who first described thromboelastography (TEG) but the method was left abandoned but was rediscovered and developed at the 50s’ – 60s’. In the

meantime, Langdell, Wagner & Brinkhous, had already presented Activated Partial Thromboplastin Time (APTT) in 1953. By the 80s', TEG was mainly used in acute haemorrhage monitoring and management, mainly in USA and in 1993, TEG® Haemonetics Corporation, IL, USA patented the method of Thromboelastography (and the relevant assays INTEG, EX-TEG, FIBTEG etc.). In 1995-7, TEM®, Munich, Germany, under the inspired leading of A. Calatzis, developed the method further and Rotational Thromboelastometry (ROTEM®, with assays as INTEM, EXTEM, FIBTEM, etc.), was initiated in 2003. The major input of Klaus Goerlinger, Essen, Germany should not be neglected mainly in developing fast response algorithms based in POC viscoelastic testing for different clinical situations.

## STANDARD LABORATORY TESTS (SLTS)

The cascade model (although now replaced by the cellular model of haemostasis) is quite useful and educational to understand the basis and the differences between standard lab tests (SLTs) and viscoelastic haemostatic assays (VHA) such as Thromboelastography (TEG®) or Rotational Thromboelastometry (ROTEM®) **Activated Partial Thromboplastin Time (aPTT)** is the time needed for plasma to clot in a matrix after activation of the “intrinsic” or contact pathway and the common coagulation

pathway. It is actually the necessary time for the haemostatic system to provide the first fibrin monomers after activation of the intrinsic pathway. Citrated plasma is being used along with added activators (like ellagic acid, silicon dioxide or kaolin) and cofactors (phospholipids and  $Ca^{2+}$ ). After an initial preincubation with the activators on a negative charged surface (from which it is often called “contact system”), plasma factor XII (FXII) is activated followed by FXI activation. The recalcification of the system leads to activation of FIX, FX, FII (prothrombin to thrombin) and finally FI (fibrinogen) to fibrin. The time spent for this sequence in seconds represents APTT. It is the pathway mainly affected by the presence of heparin or heparin like drugs.

**Prothrombin Time (PT)** represents the initiation of the “extrinsic” pathway of coagulation and is the time for plasma to clot after the addition of tissue factor (FIII) in supraphysiologic concentrations. As in APTT measurement, citrated plasma is used and mixed with heparin (to inactivate the intrinsic pathway), cofactors (phospholipids and  $Ca^{2+}$ ) and recombinant human tissue factor as activator.

**Prothrombin ratio (PR)** is the ratio of patient's PT /control plasma while **International Normalized Ratio (INR)** was introduced in an attempt to standardize the PT. In its original manifestation, the PT was very variable because different thromboplastins, necessary for the

measurement, were non-standardized and derived from many varied sources. Thromboplastin is a lab reagent equivalent to tissue factor (FIII) and can activate the extrinsic coagulation pathway. PTs performed on the identical specimen by different laboratories were inconsistent. The concept behind the INR is that differences between the thromboplastins are accounted for by a calculation:

$$\text{INR} = [\text{patient's PT} / \text{normal MNPT}]^{\text{ISI}}$$

ISI - international sensitivity index

The INR has no units (it is a ratio) and is determined to one decimal scale. The first step of the INR calculation is to “normalize” the PT by comparing it to the mean normal prothrombin time (MNPT), the geometric mean of the prothrombin times of the healthy adult population. In the second step, this ratio is raised to a power designated as the **ISI (international sensitivity index)**. The ISI is a function of the thromboplastin reagent. Two groups of data are used to derive the ISI (i) normal healthy individuals and (ii) patients stabilized on *warfarin*. Paired PT data are obtained from multiple samples using both the working thromboplastin reagent and the international thromboplastin standard. It becomes evident that INR has been developed to provide guidance for the treatment of patients receiving warfarin anticoagulants and not as mean of the global haemostatic function of the patient.

**Thrombin Time (TT)** assesses in time the final common pathway and is useful for heparin detection (indirect action) and anticoagulants detection with direct anti-FIIa (thrombin) effect (like dabigatran).

**Activated clotting/coagulation time (ACT)** is the whole blood ability to form a visible fibrin monomer in a glass tube and used in the OR or at the bedside for patients receiving intravenous heparin anticoagulation (e.g. under extracorporeal circulation or continuous haemofiltration). ACT could be considered as POC testing method assessing heparin action, protamin overdose, platelet lack/dysfunction, or factors deficiency. Nevertheless, ACT provides no specific information about the nature of the haemostatic problem like viscoelastic assays.

**Fibrinogen (FIB)** plasma levels measurement according to Clauss method, is the commonest way for fibrinogen quantitative measurement, nevertheless it is based on the thrombin Clotting Time (CT): Diluted plasma is clotted with a high concentration of thrombin at 37 °C and the CT is measured. The result is compared with a calibration curve of a reference plasma sample of known FIB concentration to give a result in g/L. Most laboratories use an automated method.

**Platelet count (PLT)** is a purely quantitative measure and cannot detect pre-existing, drug-induced or perioperative acquired PLT dysfunction.

In general, SLTs use samples of citrate plasma and not whole blood, with activators +/- cofactors and other additives,  $\text{Ca}^{++}$  (FIV), PLTs (as “activated” surfaces), FV, FVIII, Fibrinogen (FI) (as substrate) with an end point of time measurement until the first fibrin monomers formation (at the very beginning of thrombin generation). Since clot formation is completed with fibrin polymerization and stabilization, there are two “blind” spots in this type of measurement: problems or deficiency of FXIII or FvW (von Willebrand) are not covered. On the other hand, hyperfibrinolysis, one of the most common issues during acute bleeding of any pathology, is not detected, which may be detrimental if neglected.

PT, aPTT and INR are only indicative of the haemostatic disorder with no proof of haemostatic capacity and limited only at the initial first 2-5% thrombin formation in plasma, without the presence of platelets or other blood cells. Clotting times (PT, aPTT and TT) determine only the speed of thrombin generation but not the mechanical stability of the clot. They are excellent for congenital disorders detection (FVIII-, FIX- haemophilia) and very important for the urgent diagnosis of cases of acquired haemophilia. Useful in heparin detection, but may be falsely long (PT and aPTT) in cases of hypofibrinogenaemia and afibrinogenaemia. They are not designed for intraoperative bleeding disorders and are mostly performed at a

standardised temperature of 37 °C, while acute bleeding coagulopathies are very often in the context of hypothermia (as in trauma cases). Plasma fibrinogen measurement by Clauss method is not standardized and is industry dependant, absolutely quantitative and not qualitative and the same stands for platelets even if they are counted in a blood smear examination under a microscope. The cellular haemostatic component is not evident and there is no information on clot formation over time and no hyperfibrinolysis detection.

Finally, they are time consuming and have long turnaround times (40 - 90 min) which delay results, while most probably when results are available, patient’s condition is much more different from that in the moment of blood sampling.

For all these reasons the recent 2016 ESA Guidelines First Update for the management of severe perioperative bleeding recommends the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as aPTT, INR and platelet count in elective surgery. They also recommend the application of intervention algorithms incorporating pre-defined triggers and targets based on viscoelastic haemostatic assay (VHA) coagulation monitoring to guide individualized haemostatic intervention in the case of perioperative bleeding<sup>3</sup>.

## VISCOELASTIC HAEMOSTATIC ASSAY (VHA) MONITORING

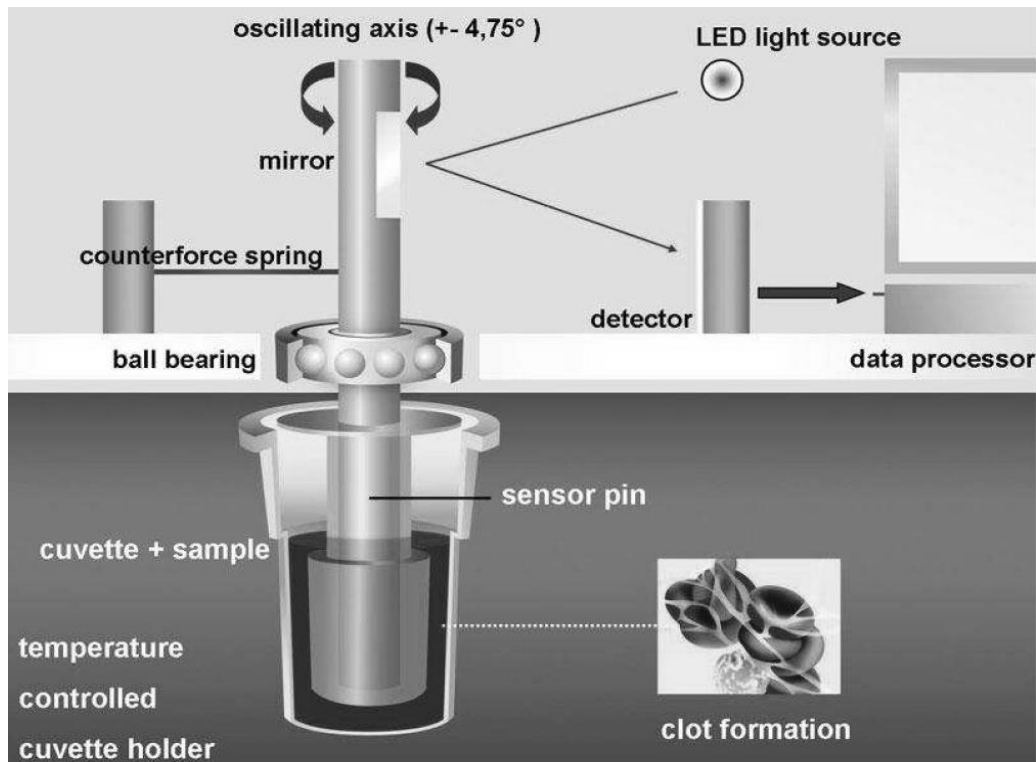
VHA monitoring like is a fast bedside (point-of-care) diagnostic approach of haemostatic derangements through whole blood viscoelastic properties assessment. VE devices provide results much more quickly (in minutes) than SLTs reflecting the cellular component of haemostasis and evaluating plasma anticoagulants. They interpret the cell-based model of coagulation, with the tissue factor (FIII) initiation of coagulation and platelet binding to collagen, followed by the propagation phase with platelet recruitment to growing thrombus and amplification of the coagulation cascade and finally, clot stabilization with platelet to platelet interaction and polymerized fibrin deposition. Moreover, normal (or abnormal) (hyper-) fibrinolysis can be detected in minutes and lead to antifibrinolytic treatment. Goal directed treatment of acute haemostatic disorders can be achieved and unnecessary transfusions may be prevented.

**Rotational Thromboelastometry (ROTEM®)** and **Thrombelastography (TEG®)** are the currently available viscoelastic test devices. Clot formation is assessed in whole blood by measuring the tensile (viscoelastic) force development between the cup (or cuvette, where the whole blood is put along with specific reagents)

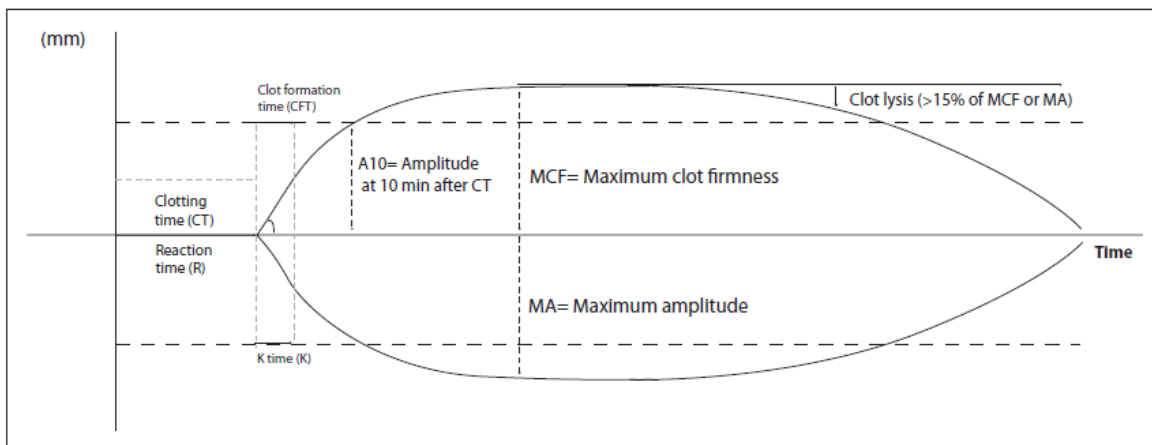
and the immersed pin. In TEG the cup rotates facilitating clot formation, while in ROTEM the cuvette remains stable and the suspended sensor pin rotates forwards and backwards, on a oscillating axis by  $\pm 4,75^\circ$ . Clot formation in the cuvette impedes free pin oscillation. This “viscoelastic signal”, created by a beam of light from a LED source falling on the oscillating pin is detected and processed to a graphical representation (i.e. thromboelastogram) of a real time clot formation (Figure 1). Thromboelastogram is highly dependent on endogenous thrombin generation, fibrin polymerization, and fibrin interactions with platelet glycoprotein IIb/IIIa receptors. In cases of systemic fibrinolysis, early clot degradation by plasmin can be observed (Figure 2)<sup>4</sup>. Both ROTEM and TEG offer similar types of tests, and yield closely related clotting measurements, but these two systems are not interchangeable because of different types of reagents and blood samples (recalcified citrated blood or fresh whole blood, accordingly). Heparinase cups are specifically requested for TEG, but the reagents for EXTEM, FIBTEM, and APTEM for ROTEM contain hexadimethrine (polybrene), which neutralizes heparin. In terms of the reference ranges, it is recommended that local values are set according to the specific patient population that is, adults or children, ethnicity, and disease types.



**Figure 1.** The principle of rotational Thromboelastometry (ROTEM®). From ROTEM-delta-and-platelet\_EN\_2016\_V01-1. ([http://top-diagnostics.com/wp-content/uploads/2017/07/ROTEM-delta-and-platelet\\_EN\\_2016\\_V01-1.pdf](http://top-diagnostics.com/wp-content/uploads/2017/07/ROTEM-delta-and-platelet_EN_2016_V01-1.pdf))



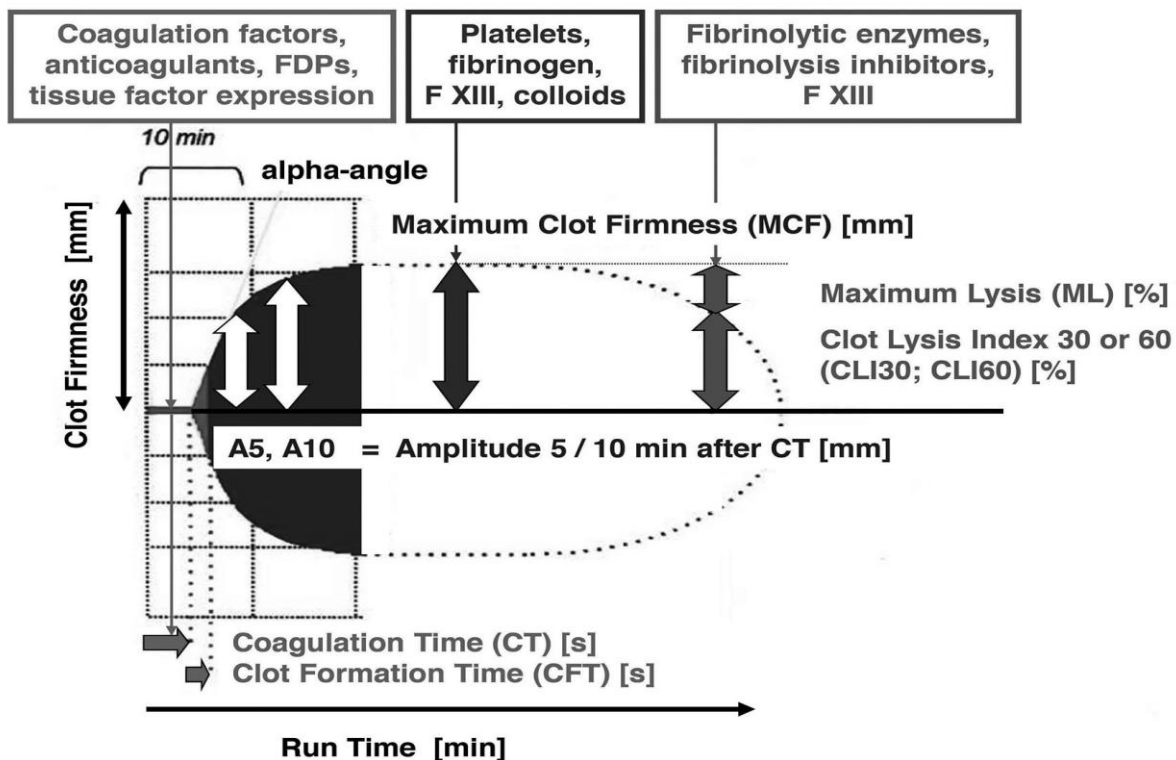
**Figure 2.** Changes in whole blood viscoelasticity are detected optically in ROTEM, and electromechanically in TEG and clot formation parameters are generated on ROTEM (upper panel) and TEG (lower panel). Plasmatic coagulation is reflected on CT and R time, and initial clot development is shown on CFT and K time (also on an angle). Maximal viscoelasticity is defined by MA or MCF for TEG and ROTEM, respectively. Systemic fibrinolysis is suspected when clot breakdown (>15% of MA or MCF) is observed within 1 h. CT, clotting time; CFT, clot formation time; MA, maximum amplitude; MCF, maximum clot firmness. Adapted with permission from reference 4.



After starting a ROTEM analysis, a typical trace is displayed providing information about clot formation (Figure 3)<sup>1</sup>. The **clotting time (CT)** reflects initial fibrin formation following thrombin generation and is defined by reaching an amplitude of 2 mm. Clot formation is further described by the time to increase amplitude from 2 mm to 20 mm (**CFT; clot formation time**) and **alpha ( $\alpha$ ) angle** (tangent of the slope). The amplitude of clot strength can be assessed 5, 10, 15, and 20 minutes after CT (**A5, A10, A15, and A20**, respectively) until the maximum amplitude is reached (**MCF; maximum clot firmness**). A5 and A10 can be used

to predict MCF reliably for early decision making. The MCF assesses the combined effect of platelet activation and aggregation, fibrin polymerization and cross-linking by FXIII. As all stages of clot formation are influenced by the activity of procoagulants and anticoagulants from clot formation to its dissolution, thromboelastometry (and thrombelastography) represents the gold standard in detecting hyperfibrinolysis. This is defined by detecting more than 15% breakdown in clot strength compared with MCF within one hour after the clotting time (ML; maximum lysis)<sup>1</sup>.

**Figure 3.** A typical thromboelastogram created by ROTEM® using citrated whole blood. Each phase of the clot formation and lysis can be used to interpret specific alterations or deficiencies of coagulation factors, anticoagulant drugs, tissue factor expression, platelets and fibrinogen participation and finally the action of the fibrinolytic system<sup>1</sup>. (See text above for more explanation)





The most notable advance in haemostatic management using viscoelastic testing is a fibrin-specific clot assessment. The system uses a combination of assays to characterize the coagulation profile for obtaining more detailed information about haemostasis and suggests the cause of the observed coagulopathy. It allows for rapid differential diagnosis between different haemostatic defects and anticoagulant drug effects. In general, the most frequently used assays are EXTEM, INTEM, FIBTEM, and APTEM. Initial screening is performed using INTEM and EXTEM assays. The addition of a contact activator (ellagic acid) provides information on the so-called “intrinsic” pathway that is comparable to aPTT measurement (INTEM assay). Extrinsic activation can be initiated by adding recombinant tissue factor, an analogue to PT measurement (EXTEM assay). Fibrin polymerization can be assessed by running an EXTEM test with the addition of a platelet inhibitor Cytochalasin D (FIBTEM assay).<sup>1</sup> The FIBTEM assay on the ROTEM allows a rapid assessment (<5–10 min) of fibrin polymerization in whole blood, and it correlates with plasma fibrinogen levels. In combination with EXTEM, FIBTEM can delineate hypofibrinogenemia from isolated thrombocytopenia, both of which decrease the overall clot strength. Heparin effects can be identified by adding heparinase to an INTEM test (HEPTEM assay) and comparing the results to the INTEM test.

Hyperfibrinolysis is suspected when the decrease of the amplitude over 1h is more than 15% of the maximum amplitude on TEG or ROTEM. To confirm hyperfibrinolysis, an EXTEM test can be performed with the addition of aprotinin which inhibits plasmin-induced fibrinolysis in vitro (APTEM assay)<sup>2</sup>. When these assays are normal, surgical bleeding rather than coagulopathy should be suspected. Alternatively, EXTEM and FIBTEM can be used mainly in clinical settings. For example, if CT in EXTEM is prolonged, prothrombin complex is given; if MCF of EXTEM is less than 40 mm and/or MCF of FIBTEM is less than 8 mm, fibrinogen concentrate is given to the patient.

Taken together, viscoelastic coagulation testing, particularly ROTEM, primarily focuses on the correction of hypofibrinogenemia, and, if any, fibrinolysis, which is followed by the correction of thrombocytopenia (or platelet dysfunction) and/or procoagulant factor deficiency. Several clinical studies have demonstrated the hemostatic effectiveness of this approach, and reduced the need for plasma transfusion<sup>5-8</sup>.

There is a distinct influence of haematocrit on ROTEM® measurements. A low haematocrit (<25%) leads to an increase in the plasma fraction of the whole blood specimen, which in turn, may result in increased FIBTEM MCF. However, the correlation between FIBTEM MCF and plasma fibrinogen levels is higher if haematocrit is decreased, and thus, the

FIBTEM assay offers an adequate method to determine fibrinogen deficiency. Bleeding patients are frequently treated with colloids, particularly with hydroxyethyl starch (HES), and this treatment has been demonstrated to have an impact on fibrinogen measurements. In the presence of HES, erroneously high levels of plasma fibrinogen have been measured using photometric assays. In this case, the ROTEM® FIBTEM test appears to be the most reliable method to detect fibrin polymerisation defects<sup>2</sup>.

## EXPERIMENTAL AND CLINICAL STUDIES

Martini et al., in an experimental study investigated the independent and combined effects of hypothermia and hemorrhage with resuscitation on coagulation in swine and evaluated clinically relevant tests of coagulation<sup>9</sup>. Hypothermia and hemorrhagic shock contribute to coagulopathy after trauma. The authors concluded that hypothermia inhibited clotting times and clotting rate, whereas hemorrhage impaired clot strength. Combining hypothermia with hemorrhage impaired all these clotting parameters. PT, aPTT were not sensitive whereas ACT was not specific in detecting these coagulation defects. Only TEG differentiated mechanism related to clotting abnormalities, and thus may allow focused treatment of clotting alterations associated with hypothermia and hemorrhagic shock.

The weakness of SLTs to estimate active coagulopathy in the course of severe perioperative bleeding has been described by Kim et al. in a study of healthy volunteers, where the authors investigated the performance and feasibility of ROTEM profile by comparing prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) results with ROTEM parameters<sup>10</sup>. They tested EXTEM and INTEM activated determinations, mainly focusing on 5 basic parameters: Clotting time (CT), clot formation time (CFT), a angle, clot formation rate (CFR), and maximum clot firmness (MCF). They compared then PT and APTT results with ROTEM parameters and observed no significant correlations between any of the ROTEM EXTEM or INTEM parameters and PT results. Only 1 parameter, the INTEM CT value, was significantly correlated with APTT results ( $r = 0.165$ ,  $P < .05$ ).

Haas et.al reviewed thoroughly and exhaustively the evidence for the continued use of standard laboratory tests (SLTs) of coagulation and their usefulness to assess coagulopathy and to guide bleeding management in the perioperative and massive bleeding setting<sup>11</sup>. Medline was searched for investigations using results of SLTs as a means to determine coagulopathy or to guide bleeding management, and the outcomes (i.e. blood loss, transfusion requirements, mortality) were reported. A total of 11 guidelines for management of massive or peri-

operative bleeding and 64 studies investigating the usefulness of SLTs in this setting were identified and were included for final data synthesis. Referenced evidence for the usefulness of SLTs was found in only three prospective trials, investigating a total of 108 patients (whereby microvascular bleeding was a rare finding). Furthermore, no data from randomized controlled trials support the use of SLTs. In contrast, numerous investigations have challenged the reliability of SLTs to assess coagulopathy or guide bleeding management. They concluded that there is actually no sound evidence from well-designed studies to confirm the usefulness of SLTs for diagnosis of coagulopathy or to guide haemostatic therapy.

In a Health Technology Assessment study, Whiting et al. examined viscoelastic point-of-care testing performing a systematic review and a cost-effectiveness analysis (PROSPERO Study)<sup>12</sup>. The study was funded by the Health Technology Assessment program on behalf of NICE (National Institute of Excellence), UK and aimed to assess the clinical and cost effectiveness of VE devices to assist with the diagnosis, management and monitoring of haemostatic disorders during and after cardiac surgery, trauma-induced coagulopathy and post-partum haemorrhage (PPH). Sixteen databases were searched to December 2013. The health-economic analysis considered the costs and quality-adjusted life-years of ROTEM and TEG

compared with SLTs in cardiac surgery and trauma patients. A decision tree was used to take into account short-term complications and longer-term side effects from transfusion. The model assumed a 1-year time horizon. Thirty-one studies (39 publications) were included in the clinical effectiveness review. Eleven RCTs assessed VE devices in 1089 patients undergoing cardiac surgery; six assessed thrombelastography (TEG) and five assessed ROTEM. There was a significant reduction in RBC transfusion [RR 0.88, 95% confidence interval (CI) 0.80 to 0.96; six studies], platelet transfusion (RR 0.72, 95% CI 0.58 to 0.89; six studies) and fresh frozen plasma to transfusion (RR 0.47, 95% CI 0.35 to 0.65; five studies) in VE testing groups compared with control. There were no significant differences between groups in terms of other blood products transfused. Continuous data on blood product use supported these findings. Clinical outcomes did not differ significantly between groups. There were no apparent differences between ROTEM and TEG. There were no data on the clinical effectiveness of VE devices in trauma patients or women with PPH. VE testing were cost-saving and more effective than SLTs. For the cardiac surgery model, the cost-saving was £43 for ROTEM, £79 for TEG and £132 for Sonoclot (a relevant device less used). For the trauma population, the cost-savings owing to VE testing were more substantial, amounting to per-patient savings of

£688 for ROTEM compared with SLTs, £721 for TEG. This finding was entirely dependent on material costs, which are slightly higher for ROTEM. VE testing remained cost-saving following various scenario analyses. The authors concluded that VE testing is cost-saving and more effective than SLTs, in both patients undergoing cardiac surgery and trauma patients. Nevertheless, subsequent studies revealed the usefulness of VE testing in PPH of several etiologies since at the beginning of labour aPTT and PT are of little predictive value for PPH<sup>3</sup>. PPH is increasingly frequent and a major contributor to maternal morbidity and mortality. Although several individual steps exist, such as coagulation or surgical management, there is little information on treatment algorithms. A treatment algorithm for postpartum hemorrhage was developed by the experts from three different specialties and from three German speaking countries (Germany, Austria & Switzerland). The algorithm, known as “DACH algorithm” describes symptoms, diagnosis, general measurements, medication, and organizational aspects<sup>13</sup>. More interestingly the FIBTEM assay evaluating the fibrinogen component of clot firmness is an early and rapidly available biomarker for predicting progression of moderate to severe postpartum hemorrhage. The traditional cut off of value of plasma fibrinogen, associated with 100% positive predictive value for PPH occurrence, is below 2 g/L

measured by the traditional Clauss method<sup>14</sup>. It seems that this can be safely and more accurately substituted by FIBTEM value in ROTEM as a rapidly available early biomarker for progression of PPH. Collins et al. in a prospective, observational study investigated the utility of FIBTEM A5 (FIBTEM value in the first 5 minutes of clot formation) and Clauss fibrinogen as predictors of progression of PPH<sup>15</sup>. A consecutive cohort of 356 women experiencing 1000 to 1500 mL PPH was recruited. FIBTEM and fibrinogen were measured and subsequent transfusions, invasive procedures, and bleed volume recorded. Women progressing to 8 U blood products (red blood cells, fresh frozen plasma and platelets) had a median plasma fibrinogen and FIBTEM A5 of 2.1 (1.8-3.4) g/L and 12 (7-17) mm, respectively, compared with 3.9 (3.2-4.5) and 19 (17-23) for those not progressing. On multivariate analysis, FIBTEM was an independent predictor for progression to bleeds >2500 mL (95% confidence interval [CI], 0.85 [0.77-0.95]). FIBTEM A5 <10 mm was associated with more prolonged bleeds and longer stay in the high-dependency unit. Our personal experience from the use of a relevant A5 algorithm based on A5 ROTEM values, facilitating decision making for transfusion triggers in the first 5 minutes of the test (K.Goerlinger, personal communication) is excellent so far.

A more relevant population with deranged and “rebalanced” haemostasis is patients with cirrhosis. Despite PT, aPTT and INR indicating coagulopathy, global coagulation tests (thrombin generation and TEG/ROTEM) suggest that haemostasis is balanced in stable chronic liver disease. In this context ESA Bleeding Guidelines discourage FFP perioperative transfusion in patients with cirrhosis.<sup>3</sup> VE testing is a valuable tool in the intraoperative management of these patients, mainly during liver transplantation. Allogeneic blood products transfusion during liver transplantation (LT) can be associated with increased morbidity and mortality. TEG®/ROTEM® information, allows creation of goal-directed, individualized treatment algorithms that may improve patient outcome. In liver transplantation such algorithms have become standard with impressive benefits: reduced transfusion needs, less complications, shorter length of ICU and hospital stay, better survival and reduced treatment costs. Kirchner et al. evaluated retrospectively the safety events observed with this approach in their clinic<sup>16</sup>. 266 LT patients were identified by chart review. A ROTEM-based algorithm with clotting factors concentrates (CFC), namely fibrinogen concentrate and/or PCC guided the haemostatic therapy. Doppler ultrasound was used to evaluate thrombosis in the hepatic artery, portal vein, and hepatic veins. Stroke, myocardial ischemia, pulmonary embolism, and transfusion variables

were recorded. 156 patients receiving CFC were included in the CFC group and 110 not receiving CFC were included in the non-CFC group. Safety events were compared between these two groups. The results showed that allogeneic transfusion(s) in the 266 patients was low, with medians of 2 (interquartile range [IQR],0-5), 0 (IQR 0-0), and 0 (IQR 0-1) units for red blood cells (RBCs), fresh-frozen plasma (FFP), and platelets (PLTs), respectively. Ninety-seven of 266 LTs (36.5%) were performed without RBCs transfusion, 227 (85.3%) without FFP, and 190 (71.4%) without PLTs. There were no significant differences in thrombotic, thromboembolic, and ischemic adverse events occurrence between the CFC group and the non-CFC group (11/156 patients vs. 5/110;  $p = 0.31$ ). The authors concluded that in LT, ROTEM-guided treatment with fibrinogen concentrate and/or PCC did not appear to increase the occurrence of thrombosis and ischemic events compared to patients who did not receive these concentrates.

In a similar retrospective study in our department we have been able to show haemostatic management following an A5 based ROTEM algorithm, reduced FFP transfusion leading to blood products administration according to the intraoperative needs, obviously reducing relative transfusion risk and cost<sup>17</sup>. We compared three successive patient groups who underwent LT. In the first group, fifteen patients were em-

pirically transfused with FFP/Blood Products (BPs) based on standard lab tests and clinical bleeding signs. In the second group, eighteen patients were transfused with FFP/BPs based on ROTEM values and in the third group, 31 patients were transfused with FFP/BPs based on a specific algorithm based on A5 ROTEM values, facilitating decision making for transfusion triggers in the first 5 minutes of the test. We found a statistically significant difference in FFP transfusion between the first two groups and the third one. Group one & two had mean values of FFPs transfused 14,93 and 11,53 units respectively, while in Group three only 4,46 units.

## CONCLUSION

Haemostatic monitoring based on SLTs is a representation of an artificial system not very close to “in vivo” situations. They are clotting times that measure the enzymatic activity of coagulation factors from a starting signal until the formation of fibrin (stopping signal). They have two main indications: Detection of factor deficiencies (congenital/acquired) and anticoagulant treatment monitoring. They also suffer from two blind spots (FXIII & FvW assessment), but in this case, it may be covered by other special tests. Their main weakness is that they interpret only the “cascade” model of the coagulation procedure, reinstated as an artificial system (no cells;  $Ca^{2+}$ , pH and temperature are not accounted for) and with long turnaround

time. In the surgical setting of perioperative coagulopathy (i.e. trauma, cardiac, liver surgery, obstetric PPH, etc.), SLTs offer no prediction, no detection and no coagulation management guidance. On the contrary, Viscoelastic Haemostatic Assays are a Point-of-Care monitoring procedure offering the most promising support in early and individualized decision making for the correct type and quantity of blood product/factor/substitute needed to be transfused with impact in overall morbidity, mortality and cost.

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