3

Perioperative coagulation monitoring

Sibylle A. Kozek-Langenecker, MBA, Dr. Prof\textsuperscript{a,b,*}

\textsuperscript{a} Department of Anaesthesiology, General Intensive Care and Pain Management, Vienna Medical University, Währinger Gürtel 18-20, 1090 Vienna, Austria
\textsuperscript{b} Department of Anaesthesia and Intensive Care, Evangelisches Krankenhaus Wien, Hans Sachs-Gasse 10-12, 1180 Vienna, Austria

Keywords:
bleeding history
activated partial thromboplastin time
prothrombin time
rotational thrombelastometry
platelet function analyser
platelet aggregometry
activated clotting time

Perioperative coagulation monitoring is the rational diagnostic basis for pro- and anti-thrombotic interventions in patients undergoing emergency and elective surgery. The main goal of perioperative monitoring of haemostasis is to increase safety of patients undergoing surgical procedures. Currently, there is a change in paradigm with (1) increasing implementation of evidence-based approach to preoperative patient evaluation with laboratory coagulation testing secondary to the results of the standardised bleeding history and (2) awareness of the limitations of routine coagulation tests to guide coagulation management in massive bleeding. Alternatively, visco-elastic point-of-care monitoring is increasingly used worldwide. This innovative methodology triggers a trend towards an ‘early goal-directed coagulation management’ focussing on potent coagulation factor concentrates. Practicability, cost-effectiveness, safety and – above all – growing scientific evidence support this concept, and lively discussions among anaesthesiologists and various medical disciplines may help to refine it. The present review focusses on the following key issues of perioperative coagulation monitoring:

- standardised bleeding history,
- routine coagulation testing,
- visco-elastic point-of-care coagulation testing,
- heparin monitoring and
- platelet function testing.

© 2009 Elsevier Ltd. All rights reserved.
Preoperative evaluation

The aim of pre-operative coagulation testing is to detect patients' characteristics that may be associated with increased perioperative bleeding: Coagulation disorders with a high prevalence (e.g., von Willebrand disease), rare disorders with high clinical relevance (e.g., coagulation factor deficiency in haemophilia) as well as drug-induced coagulopathy (e.g., dual anti-platelet therapy and vitamin K antagonists). There is growing evidence that the traditional diagnostic pathway involving routine coagulation screening tests is not reliable in identifying patients at risk for bleeding or thrombosis during surgical interventions, as well as in predicting and preventing these adverse outcomes.\textsuperscript{1–4}

Standardised bleeding history

The preoperatively assessed bleeding history of the patient and of his/her relatives remains the most important tool for detection of both mild and severe inherited or acquired bleeding disorders, which may increase the risk of perioperative bleeding.\textsuperscript{5} Standardised questionnaires have been designed to assess the type of bleeding (mucosal vs. non-mucosal) and the timing of bleeding (immediate vs. delayed, since early childhood vs. late in life) among other items such as use of anti-coagulant or anti-platelet drugs.\textsuperscript{6,7}

Relevant items of a standardised questionnaire are:

- **Known coagulopathy** (bleeding history of the patient and relatives indicating severe bleeding diathesis)
- **Epistaxis** without obvious reasons
- **Haematoma, petechia** at torso/unusual location without other reasons
- **Wound-healing defects**
- **Prolonged bleeding** after abrasion/cut, during or after previous surgery, during or after teeth extraction
- **Abnormal blood and blood product requirement** after previous surgery
- **Hypermenorrhagia** requiring more than seven tampons per day, bleeding for more than 7 days since menarche
- **Medication affecting coagulation**: pain killers, anti-thrombotic and anti-platelet drugs, over-the-counter drugs and dietary factors.

If one item is answered by ‘yes’, the bleeding history is defined as abnormal. In an adult patient population, bleeding history was abnormal in about 11%.\textsuperscript{6}

Practice points

- Bleeding history should be assessed well in advance before elective surgical procedures to have time for further diagnostic, logistic and therapeutic consequences.
- The patient, his/her relatives or guardian fills in the questionnaire, and later the anaesthetist (or the anaesthetist in training under supervision) validates the information.
- In case of language barrier, lack of compliance or intellectual disabilities of the patient, first-level laboratory test should be performed together with clinical examination and interviewing relatives about the patient's bleeding history and medication. This process is also recommended in emergency surgery (combined with point-of-care coagulation testing described below).

Clinical examination

Preoperative clinical examination is recommended because it may objectively reveal haematoma, petechia or wound-healing defects, indicating bleeding disorders even in unconscious or incompetent
patients. Examination for bleeding symptoms should be performed as a standardised procedure during routine preoperative patient evaluation.

Preoperative laboratory testing

If bleeding history is normal, further laboratory investigations of haemostasis are only indicated if the patient is scheduled for surgery with a high risk of bleeding or if there is a relevant comorbidity.8 If bleeding history is abnormal, further laboratory investigation of haemostasis is indicated, and this requires a stepwise approach.9 Recommended baseline screening tests involve the routine coagulation tests investigating the plasmatic coagulation profile, as well as tests allowing analysis of primary haemostasis capacity.6 Pathological test results require further diagnostic, logistic and therapeutic consequences10 aimed at risk reduction as well as medico-legal considerations (e.g., informed consent).

Intra-operative monitoring

The aim of intra-operative coagulation testing is to detect the pathomechanisms of increased perioperative bleeding to initiate treatment rapidly. Haemostatic competence is one of the three mainstays in blood-sparing medicine.11

Clinical view and confounders

Periodic visual assessment of the surgical field and communication with the surgical team are recommended as standard practice to detect impending or established coagulopathy, and entails the assessment of the amount of blood lost and the presence of microvascular bleeding from mucosal lesions, serosal surfaces, catheter insertion sites and wounds. The diagnosis of intra- and postoperative coagulopathy in massive transfusion needs to be verified by appropriate coagulation tests.5 Meanwhile, surgical attempts to control a visible source of haemorrhage are required (e.g., ligation, embolisation and packing). Monitoring further includes temperature monitoring for maintaining normothermia and blood gas analysis for correction of acidosis, anaemia and hypocalcaemia.

Routine coagulation testing

Although these tests were not developed to predict bleeding or to guide coagulation management in the surgical setting, most centres in clinical practice draw blood perioperatively for the following routine coagulation tests (‘routine coagulation panel’):

Research agenda

- Further research is warranted to ensure that preoperative patient evaluation using an algorithm involving a standardised bleeding history, physical examination and a stepwise laboratory testing followed by patient optimisation improves not only blood loss and transfusion requirements, but also morbidity and mortality in perioperative patients.
- Cost-effectiveness of such a preoperative algorithm needs to be evaluated. Considering the high number of patients with normal bleeding history undergoing surgery with low bleeding risk, avoidance of unnecessary laboratory testing is suggested to contribute to significant reductions in health-care costs.
Activated partial thromboplastin time (aPTT): The aPTT was developed to monitor heparinisation in the treatment of thrombo-embolic disorders, to characterise clotting factors and for research on haemophilia. Activation of coagulation factors, formerly known as ‘intrinsic coagulation cascade’, is performed by incubating plasma with partial thromboplastins, calcium and kaolin powder at 37 °C at a standardised pH. The endpoint of measurement is the formation of fibrin strands. Standardisation, however, is difficult due to the large variation in calibration constants and methods of endpoint detection, as well as the wide range of pro- and anticoagulant factors affecting aPTT results. The aPTT is sensitive to coagulation factors VIII, IX, XI, XII, V, II and I; heparin; fibrinogen degradation products; inhibitors, hypothermia; and hypofibrinogenaemia. Multiple-factor deficiencies tend to show a greater prolongation for a given factor level than single-factor deficiencies. The empiric cut-off value for therapeutic intervention fresh frozen plasma (FFP) or prothrombin concentrate (PCC) in major surgery is an aPTT >1.5–1.8 above normal upper limit (>60 s).

Prothrombin time (PT): This test was developed to monitor and adjust the doses of coumarins. Activation of coagulation factors, formerly known as ‘extrinsic coagulation cascade’, is performed by incubating plasma with tissue thromboplastin and calcium at 37 °C at a standardised pH. The time until fibrin strand formation is determined. This test is sensitive to coagulation factors II, VII, X, V and I. Standardisation of the PT for laboratory control of oral anticoagulant treatment is based on the responsiveness of one type of thromboplastin, measured by its international sensitivity index and conversion into the international normalised ratio (INR). Direct INR determination is performed by local calibration using plasma of certified levels of PT. The empirical cut-off value for therapeutic intervention (FFP or PCC) is a PT below about 40%.

Platelet count: Platelet counting is routinely performed by automated machines. The number of platelets, however, does not reflect the quality of platelet function. The empirical cut-off value for platelet transfusion is platelet count <50–100 G l⁻¹.

Fibrinogen concentration: Fibrinogen plays a major role in routine coagulation tests such as PT and aPTT. There are two methods used in specific fibrinogen assays: (1) determination of the amount of fibrinogen molecules per se, for example, by immunologic, gravimetric or heat precipitation and (2) determination of clottable fibrinogen. In the conventional Clauss method, where thrombin is added to plasma, the fibrinogen concentration is proportional to the coagulation time measured. This test is affected by heparin and fibrinogen degradation products. Excessive bleeding has been reported at fibrinogen levels below 50–100 mg dl⁻¹, but evidence is accumulating that much higher levels of fibrinogen are required for sufficient fibrin clot polymerisation with target levels at 200–380 mg dl⁻¹.

Second-level coagulation tests: Because of long turnaround times and limited availability in many laboratories, coagulation factor levels and molecular markers of the coagulation and fibrinolytic system are rarely assayed in the acute preoperative setting. Patients with inherited coagulation defects may exsanguinate with trauma or major surgery unless specific factor replacement is provided (such as factor VIII, IX and von Willebrand factor concentrate) necessitating second-level coagulation tests.

Limitations of routine coagulation tests in the perioperative setting

In the perioperative setting where events may proceed at a fast and dramatic pace, real-time monitoring of the patient’s coagulation profile and repeated laboratory tests are vital in administrating proper replacement therapy. However, test results of routine coagulation monitoring performed at the hospital’s central laboratory are generally only available with a delay of at least 30–60 min (sample preparation including centrifugation and buffering, transportation of blood samples and test results). Hardy et al. concluded that bedside monitors of haemostasis are needed urgently for the management of operative and trauma-associated bleeding. The bedside test of PT and aPTT in whole blood using the CoaguCheck (Roche Diagnostics, Switzerland), aimed at overcoming this limitation, however, correlates inadequately with central laboratory test results.

The most important limitation of routine coagulation tests is the fact that the predominant pathomechanism of bleeding in the complex scenario of trauma-associated coagulopathy or massive intraoperative blood loss cannot be differentiated: prolonged aPTT may be due to ‘intrinsic coagulation factor’ deficiency requiring specific substitution, fibrinogen deficiency requiring fibrinogen substitution, hypothermia requiring re-warming, heparinisation requiring protamin reversal or...
hyperfibrinolysis requiring anti-fibrinolytic drugs. Thus, a false differential diagnosis may lead to therapeutic misadventures. Due to the complex nature of haemorrhage in this setting, physicians require coagulation monitoring strategies sensitive to all major possible pathomechanisms. Near-patient (point-of-care) coagulation monitoring devices have become available and are likely to overcome several limitations of routine coagulation testing.

Routine coagulation tests are performed in plasma at a standardised temperature of 37 °C, without the presence of platelets and other blood cells. Accordingly, routine laboratory tests cannot assess the effect of hypothermia on haemostasis in hypothermic patients. Furthermore, fibrinolysis and platelet dysfunction pose diagnostic gaps. Since the haemostatic response to injury or surgery is a complex interaction of plasma proteins, platelets and the vessel wall, according to the present well-accepted cell-based model of haemostasis, it cannot be determined by tests performed in plasma. Although aPTT, PT, fibrinogen concentration and platelet count determination are well validated and accepted, methodological problems include variable sensitivity of test reagents, high variability between labs and investigators, as well as insufficient standardisation. Fibrinogen level determination by Clauss method may be false high in the presence of synthetic colloidal solutions, especially hydroxyethyl starches, which are clinically required for fluid resuscitation.

Routine tests pick up abnormalities in haemostasis due to single or multiple deficiencies in coagulation factors, but do not identify them. PT and aPTT assess only the speed of fibrin strand formation, but not the mechanical and functional properties of the clot over time. Functional fibrin polymerisation may be impaired despite normal fibrinogen concentration.

Routine coagulation tests are poor predictors of bleeding and mortality: Severe aPTT prolongations >1.8 times normal are associated with bleeding. Similarly, INR elevations in trauma patients are only indicative for risk of generalised bleeding if they are >1.5–1.8 times normal and are associated with an elevated aPTT. A severely prolonged activated clotting time (ACT) may indicate exhaustion of the coagulation system’s reserve. In trauma victims, an initially abnormal PT increases the adjusted odds of mortality by 35%, a prolonged aPTT by 326%. Several studies demonstrate a poor correlation between the amount of blood products given and the severity of coagulation defects. Obviously, simplistic formulas or flow charts for predicting factor deficiencies from blood loss are not applicable. Although severely abnormal PTs and aPTTs are predictors of mortality, the poor predictive power of moderately impaired routine coagulation tests has repeatedly been argued as a major limitation. In a multiple regression model, platelet count was not an independent predictor of mortality in emergency medicine. The decline of platelet count is a highly individual phenomenon; some patients are even able to recruit platelets from storage pools. Most patients approach the critical platelet count after losing two blood volumes.

Each routine test is specific for some portion of the haemostatic mechanism, and none can stand alone. The costs for the laboratory test panel of PT, aPTT, platelet count and fibrinogen are higher than the costs for single tests.

**Practice points**

- Limitations for routine coagulation tests in clinical management of perioperative bleeding are:
  - delays in test result reporting,
  - insufficient differential diagnosis of complex acquired intra-operative coagulopathy,
  - insensitivity for function of fibrinogen, hyperfibrinolys and platelet dysfunction,
  - methodological limitations,
  - poor predictors of bleeding and mortality,
  - still in use due to tradition rather evidence,
  - artificial test milieu not accounting for the cell-based physiology of haemostasis and
  - direct costs for panel analyses need to be considered.
Thromboelastography (TEG) and rotational thromboelastometry (ROTEM)

The visco-elastic whole blood test was invented by Hartert in 1948, and it has been included in the panel of laboratory monitoring for coagulopathy by the American Society of Anaesthesiologists. TEG and ROTEM measure the visco-elastic properties of non-anticoagulated or (citrate) anticoagulated blood after induction of clotting under low shear conditions, resembling the rheologic properties in venous vessels in vivo. The pattern of changes in visco-elasticity reflect the kinetics of all stages of thrombus formation (r and k time, CT and CFT), the stability and firmness of the clot, which is a function of platelet–fibrin interaction and fibrin polymerisation (MA, MCF), as well as dissolution (fibrinolysis). Interpretation of TEG/ROTEM results is simplified by both graphical and numerical presentation of results, highlighting of abnormal results and computerised analysis of the trace. Test principle of ROTEM is explained in Fig. 1.

ROTEM (Pentapharm GmbH, Germany) improved the original TEG (Haemoscope Inc., USA) procedure by reducing the interference with vibrations and limited transportability. Furthermore, ROTEM not only provides a global picture of the injured patient’s haemostatic status but also permits differential diagnosis of the major underlying pathomechanism of coagulopathy by implementing test modifications.

Test modifications of ROTEM and differential diagnosis of bleeding

Addition of different coagulation-activating agents and/or platelet-inhibiting agents allows the detection and quantification of specific coagulation defects such as defect in clot firmness due to fibrinogen deficiency (being an early phenomenon) and thrombocytopenia, prolonged clot generation

![Fig. 1. Test principle of rotational thromboelastometry (ROTEM). Citrated whole blood, native whole blood or plasma (300 µl) and test reagents are pipetted semi-automatically into a single-use plastic cup that is set onto a plastic pin on a rotating vertical axis (±4.75°) guided by ball bearings. The increasing firmness of the clot gradually reduces the movement of the pin. This is continuously detected by using a light source, a reflecting mirror on the rotating axis, and a detector chip. The reduction in movement is mathematically transformed into clot firmness (amplitude in millimetres) and plotted against time (in seconds), resulting in a thromboelastometric trace.](image-url)
due to various coagulation factor deficiencies or heparin and impaired clot stability due to hyperfibrinolysis and factor XIII deficiency (being a late phenomenon).  

**EXTEM** is a baseline test that uses recombinant tissue factor to activate coagulation (comparable to the PT), which causes rapid generation of the clot. The maximum clot firmness ($MCF_{\text{EXTEM}}$) gives information on the maximum clot strength and stability, which is largely dependent on platelet count and fibrinogen level. Prepared disposable wells containing cytochalasin D, a platelet inhibitor, are used in the **FIBTEM** test. $MCF_{\text{FIBTEM}}$ represents the contribution of fibrinogen to the clot strength. Critical MCF cut-off values appear within about 15 min after test initiation (depending on haemostatic function). A low $MCF_{\text{FIBTEM}}$ is indicative for administration of fibrinogen concentrates. A normal $MCF_{\text{FIBTEM}}$ ($\geq 12$ mm) in the presence of a low $MCF_{\text{EXTEM}}$ (<50 mm) indicates the need for platelet substitution.  

Thus, comparing $MCF_{\text{FIBTEM}}$ with $MCF_{\text{EXTEM}}$ permits differentiation of a low platelet count from dys- or hypofibrinogenaemia. Some experts recommend analysis of A10 (clot strength 10 min after the start of ROTEM) instead of the MCF because this parameter is obtained even faster. This approach allows timely therapeutic decisions. $A10_{\text{FIBTEM}} < 7$ mm triggers administration of high-dose fibrinogen concentrate (25–50 mg kg$^{-1}$).  

The clotting time ($CT_{\text{EXTEM}}$) gives information about the initial activation and dynamics of clot formation, thus allowing analysis of factor deficiencies. The critical cut-off value for CT, indicating the necessity to administer PCC (20–30 IU kg$^{-1}$) or FFP (30 ml kg$^{-1}$), appears about 100s after test initiation.  

EXTEM allows for the visual diagnosis of hyperfibrinolysis when a typical tapering trace is shown. In addition, wells containing aprotinin (APTEM) permit the quantitative assessment of fibrinolysis and the estimation of the therapeutic benefit from antifibrinolytic agents such as tranexamic acid. Any improvement in CT, CFT and MCF in APTEM compared with EXTEM de-masks low-grade hyperfibrinolysis (e.g., $CT_{\text{APTEM}}/CT_{\text{EXTEM}} < 0.8$). Risks associated with antifibrinolytic drugs have to be considered. If detected in the ROTEM or TEG, hyperfibrinolysis has to be corrected first (by administration of antifibrinolytic drugs) followed by replacement of the consumed coagulation factors.  

**INTEM** uses ellagic acid contact activator (comparable with the reagent used for aPTT) to analyse the general coagulation status. Wells containing heparinase (HEPTEM) or ecarin can be used to detect specific anticoagulant effects.

---

**Practice points**

- ROTEM with its test modifications proves very helpful in decision making and the treatment of massive bleeding.
- FIBTEM and EXTEM should be performed simultaneously as first-line ROTEM tests in bleeding surgical patients.
- INTEM and HEPTEM should be performed as first-line ROTEM tests in heparinised (cardiac) patients and as second-line ROTEM tests in all other surgical patients if (endogenous or exogenous) heparinisation is suggested to complicate bleeding.
- Standardised operating procedures required for quality control testing are available. A multicentre investigation yielded consistent values between centres and provided general orientating reference ranges for the ROTEM.
- Normal visco-elastic test results are unlikely to coincide with bleeding (high negative predictive value). As a consequence, another important implication of TEG/ROTEM monitoring is the immediate initiation of surgical re-exploration if no haemostaseological cause of bleeding is observed.
- The motto of coagulation management in the bleeding patient is to replace what is missing. Individualised and efficient intervention requires timely and sensitive coagulation monitoring at the point-of-care.
- TEG/ROTEM measurements should be performed at baseline of surgery, when clinically abnormal bleeding occurs and after therapeutic interventions. Tests should be initiated immediately after blood withdrawal to permit point-of-care management.
TEG/ROTEM measurements can be performed at the actual body core temperature of the patient at adjusted test temperatures between 22 °C and 42 °C, thus allowing quantitative analysis of the anti-coagulant effect induced by hypothermia. Test temperature adaptations, however, are impractical in the OR because physicians may be tempted in treating abnormal test results with coagulation factor substitution whereas only re-warming is indicated.

Management-algorithm for coagulation therapy

Perioperative coagulation testing is only useful if test results are implemented into clinical decision making. A management algorithm for coagulation therapy is a systematic definition of decisions based on laboratory data, patient- and procedure-specific issues.19 Routine laboratory-based transfusion algorithms still are superior to treatment solely based on the clinician’s experience and estimating blood loss.17,35 The institution of transfusion algorithms based on thromboelastographic parameters reduced transfusion requirements (and in some study designs also blood loss) in both routine and high-risk cardiac surgery (in adults and children) and liver transplantation.36–43 Transfusion requirements before and after the implementation of ROTEM were statistically significantly lower and clinically more accurate.44 Recommendation to use visco-elastic point-of-care coagulation monitoring embedded into a management algorithm is high.

Research agenda

- Head-to-head comparison between management algorithms based on routine coagulation tests and near-patient monitoring would be desirable, but may never become available, because departments that switched to ROTEM often regard a routine laboratory test group as unethical and impractical.

Limitations of point-of-care algorithms based on TEG/ROTEM

When performed by anaesthesiologists or nursing personnel within the OR or the trauma unit, the possibility for handling mistakes and false data interpretation have to be considered. Point-of-care monitoring with ROTEM is still an evolving field. Concomitant training, education and quality control are critical. Because of the inability to detect platelet function disorders such as von Willebrand syndrome and anti–platelet drug effects (except for the novel TEG aggregation test Platelet Mapping™ Assay), it is recommended to perform more specific tests in platelet-dependent bleeding. ROTEM test combinations (EXTEM + FIBTEM) are required as a basic panel in massive bleeding. However, cost savings by the ROTEM-based early goal-directed coagulation management are significant in clinical practice, because it helps to shorten surgical procedures, lowers the frequency of re-openings, shortens the stay in the ICU and minimises the direct costs of blood products and costly adverse effects of transfusion.45,46

Practice points

Limitations for ROTEM in the clinical management of perioperative bleeding are:

- requirement for training, education and quality control;
- insensitivity for platelet dysfunction and drug monitoring (e.g., vitamin K antagonists); and
- direct costs for panel analyses need to be considered.
**Point of care: definition**

Point-of-care monitoring in laboratory medicine is defined as a test requiring only one single pipetting step. In perioperative medicine, however, the term point-of-care monitoring is used for all tests that can be performed at the bedside (outside the hospital’s central laboratory) also by non-laboratory personnel for timely therapeutic interventions. Alternatively, performance of TEG/ROTEM in the central lab by trained laboratory personnel reduces the possibility for handling mistakes; on-line data transmission to a monitor in the OR is a prerequisite for early goal-directed coagulation management.

Perioperative bleeding patients are managed routinely by anaesthesiologists who evolved into experts in intra-operatively acquired coagulation management. Point-of-care coagulation monitoring using TEG/ROTEM increases knowledge and vigilance of anaesthesiologists for haemostasis and coagulopathy. It may be very helpful to assign a haematologist or transfusion specialist to a multidisciplinary team treating acutely bleeding patients, if proper blood component therapy cannot be achieved by the OR unit team, including anaesthesiologists trained in coagulation management and point-of-care monitoring. Interdisciplinary user meetings, symposia and e-learning projects further promote the exchange of experience and speed up transfer of knowledge. Interdisciplinary definition of a hospital-specific management algorithm may facilitate patient care.

**Intra-operative heparin monitoring**

Intra-operative quantification of unfractionated heparin effects during full heparinisation such as during cardiopulmonary bypass is traditionally performed by the ACT. Various ACT devices are currently available, but all are fundamentally based on the test principle of aPTT. Reference ranges are poorly standardised and dependent on activators (e.g., kaolin and celite) and test media (e.g., plasma and whole blood). ACT measurement using, for example, the Hemochron microcoagulation system is a true point-of-care monitoring.

ACT is not sensitive enough to monitor low heparin doses, for example, for protection of difficult vascular anastomoses. In these situations, aPTT or thrombin time (TT) is recommended. For TT, citrated plasma is incubated only with thrombin. The endpoint of measurement is the formation of fibrin strands. TT is sensitive to heparin, anti-thrombins, fibrinogen degradation products and hypofibrinogenaemia.

TEG/ROTEM assays with and without heparinisation (HEPTEM test) permit quantification of heparin effects at low and high concentrations, as well as estimation of the therapeutic benefit from protamin reversal by comparing CT\_INTEM and CT\_HEPTEM. CT\_INTEM > 240 s and CT\_HEPTEM/CT\_INTEM < 0.66 triggers protamin administration.

Sonoclot Coagulation and Platelet Function Analyser (Sienco Inc.), Arvada, Colorado, USA is a viscoelastic monitoring technique. This test provides information on the entire haemostasis process, including fibrin gel formation, clot retraction and fibrinolysis, comparable with TEG/ROTEM. The Sonoclot Analyser generates both a qualitative graph (Sonoclot signature) and quantitative results on the clot formation time (ACT – onset) and the rate of fibrin polymerisation (clot rate). The currently available test kits containing activators such as kaolin, celite and glass beads indicate the main indication for Sonoclot Analyser in ACT–heparin monitoring in cardiac surgery. For perioperative bleeding patients, no test kits comparable with the FIBTEM, EXTEM and APTEM are available, which currently limits its applicability into goal-directed management algorithms.

**Platelet function tests**

Widespread adoption of anti-platelet agents into everyday clinical practice has revolutionised contemporary care of cardiovascular patients. The peri-operatively bleeding risks posed by these drugs
Fig. 2. Impedance aggregometry using the Multiplate. Whole blood (300 μl) and agonists at standardised concentrations (collagen (COLLtest), arachidonic acid (ASPItest), adenosine diphosphate (ADPtest), thrombin receptor activator peptide 6 (TRAPtest), ristocetin (RISTOtest)) are pipetted semi-automatically into a single-use plastic cup with a pair of electrodes and a stirring bar. Platelet adhesion and aggregation change electrical impedance between the electrodes. This is continuously detected and transformed, resulting in an aggregometric trace with the parameters of aggregation velocity, maximum aggregation and area under the aggregation curve. Bottom panel: normal aggregation response in TRAPtest (left), aggregation inhibition in an aspirin responder in ASPItest (middle), aggregation inhibition in a clopidogrel responder in ADPtest (right). Parameters of Multiplate are indicated: maximum aggregation, aggregation velocity and area under the curve (AUC).
will become increasingly important.\textsuperscript{49,50} Platelet function tests are the first-level tests in the preoperative evaluation of patients with positive bleeding history\textsuperscript{6,51} (Fig. 1) and the second-level tests in actively bleeding patients if anti-platelet therapy, inherited or acquired platelet defects or extracorporeal circulation is involved, and if ROTEM and ‘routine coagulation panel’ tests cannot reveal a defect in haemostasis responsible for bleeding.

There is still no simple reliable method for measuring platelet function. Static tests such as the measure of β-thromboglobulin capture only one single point in time and cannot accurately reflect the dynamic processes encountered intra-operatively. Dynamic tests such as the \textit{in vivo} bleeding time reflect the time-dependent contribution of platelets to overall clot formation. However, the \textit{in vivo} bleeding time is an old test method in which the time until cessation of bleeding after incision of the skin by a specific device is determined. \textit{In vivo} bleeding time is poorly standardised, temperature and drug dependent (catecholamines), influenced by vascular disorders, lacks specificity and sensitivity and is not predictive of bleeding.\textsuperscript{52} The bleeding time increases unspecifically during surgery and transfusion\textsuperscript{53} and does not allow the differentiation between bleeding and non-bleeding patients.\textsuperscript{22}

Several modern platelet function analysers on the verge of clinical implementation test the platelet’s response to an agonist. The Platelet Function Analyser PFA-100 (Dade) provides a measure of platelet function in citrated whole blood. The device measures platelet function at high shear rates. The blood sample (800 μl) is added to a reservoir well in a disposable cartridge. The instrument aspirates the blood sample under constant vacuum through a capillary and the microscopic aperture within a membrane coated with platelet agonists, collagen and either epinephrine or adenosine diphosphate (ADP). This leads to the attachment, activation and aggregation of platelets forming a plug. The time taken to occlude the aperture is known as ‘closure time’ and is a function of platelet count and reactivity, von Willebrand factor activity and haematocrit.\textsuperscript{54} This method rapidly identifies aspirin effects and platelet disorders prior to surgery.\textsuperscript{6,51,55} Therefore, the PFA-100 has gained acceptance in the identification of the von Willebrand syndrome.

In patients with preoperatively identified platelet dysfunctions and without contraindications against desmopressin, shortening of the PFA closure time after desmopressin infusion should be assessed (‘desmopressin response test’). In cardiac surgical patients, the preoperative PFA-100 closure time correlated with postoperative blood loss in some studies\textsuperscript{56}, but not in others.\textsuperscript{57} A Medline search on the use of the PFA-100 during massive transfusion failed to retrieve any relevant references. Major limitations of the PFA-100 as an intra-operative point-of-care system in massive transfusion include its strong dependence on platelet count (>100 G l\textsuperscript{-1}) and haematocrit (>30%). Normal values are PFA-closure time <165 s in epinephrine cartridges and <186 s in ADP cartridges.

Optical and impedance platelet aggregometry assess platelet reactivity by measuring changes in luminescence or impedance upon platelet agonist stimulation. Originally, these techniques have only been performed in specialised laboratories by experienced technicians. The need for time-consuming preparation of platelet-rich plasma at a certain number of platelets limited widespread application of optical aggregometry (Born aggregometry). Further limitations were temperature dependence, stirring rate and limited standardisation. Nevertheless, optical aggregometry remains the accepted ‘gold standard’ for the detection of platelet function until now. The novel impedance aggregometer Multiplate (Dynabyte) is a significant step forward and avoids several methodological problems of the original platelet aggregometry, especially by using whole blood, disposable test cuvettes, various commercially available test reagents at standardised concentrations (e.g., collagen, arachidonic acid, ADP, thrombin receptor activating peptide 6 TRAP and ristocetin), semi-automated pipetting system and a direct thrombin inhibitor as anticoagulant with minimal \textit{per se} effects of platelet function. The test principle of Multiplate is shown in Fig. 2. Sample reading time is 3–6 min.

This device has been used successfully in the detection of anti-platelet drugs\textsuperscript{58–60} and of changes in platelet function after cardiac surgery.\textsuperscript{59,61,62} Impedance aggregometry could potentially provide point-of-care differential diagnostic information required for evidence-based therapy in acute bleeding problems.\textsuperscript{36,47} However, the Multiplate assay has not been validated for low platelet counts and, thus, its use in haemorrhagic thrombocytopenia remains to be determined. Other platelet-monitoring techniques assessing the platelet’s response to various agonists are emerging such as Hemostatus (Medtronic), Rapid Platelet Function Analyser (Ultegra, Accumetrics), Clot Signature Analyser (CSA; Xylum), PlateletWorks (ICHOR, Helena Bio Sience), Hemodyne Platelet Analysis System (Hemodyne...
In summary, pre-operative coagulation monitoring includes assessment of a standardised bleeding history and laboratory testing including plasmatic coagulation and primary haemostasis capacity if history is abnormal or procedure-specific risk factors for bleeding are anticipated. This evidence-based approach identifies patients at risk for perioperative bleeding and permits preoperative optimisation leading to risk reduction.

For intra-operative heparin monitoring, various tests such as ACT, aPTT, TT and viscoelastic tests are available.

In massively bleeding patients, routine coagulation tests such as aPTT and PT have major limitations to guide management. Clinical experience clearly indicates that time lost while waiting for routine lab results aggravates coagulopathy, bleeding, blood product requirements, time of surgery and morbidity. This important issue of timing appears unanswerable by controlled trials because it is unethical to withhold procoagulants for defined period of times and watch the bleeding. Instead, point-of-care coagulation tests deliver indicative test results within minutes and permit an early goal-directed intervention. While TEG and Sonoclot Analyser describe a global picture of the haemostatic process, ROTEM extends this feature by a test kit repertoire permitting differential diagnosis of major pathomechanisms of intra-operatively acquired coagulopathy. Critical questions on sensitivity, practicability, validation and cost-effectiveness have already been answered. The effect of point-of-care monitoring on improved mortality remains unanswered.

**Practice points**

- PFA-100 and impedance aggregometry (Multiplate) can be performed near the patient with short sample reading times of <6 min.
- Indication for PFA-100 testing is the preoperative detection of the von Willebrand syndrome.

Limitations for platelet function monitoring in the clinical management of perioperative bleeding are:

- pre-analytical standardisation (e.g., withdrawal without stasis, resting time of sample until analysis, anti-coagulant in test cuvette and no cooling/freezing of samples);
- methodological limitations;
- requirement for training and education for appropriate interpretation; and
- direct costs need to be considered.

**Research agenda**

- Large-scale clinical studies are required to reassure that impedance aggregometry (Multiplate) has an indication for perioperative drug monitoring of aspirin and clopidogrel. Procedure-specific critical cut-off values and predictive power for predicting bleeding and mortality need to be established.
- Future studies will have to evaluate if Multiplate may assist in platelet function monitoring after extracorporeal circulation and as second-level tests in cases were ROTEM and/or routine coagulation tests cannot reveal a defect in haemostasis responsible for bleeding considering the limitation in thrombocytopenia.

Inc.), Platelet Mapping Assay (Haemoscope) and Cone and Plate Analyser (CPA “Impact”; Diamed). These tests as well as flow cytometric assays have not yet been broadly adopted in the treatment of platelet-related perioperative bleeding.
Conflicts of interest statement

The author received honoraria for lecturing and funding for the academic, non-profit educational e-learning platform www.perioperativebleeding.org from companies involved in perioperative coagulation monitoring (Dynabyte, Pentapharm).

References


